LUND UNIVERSITY

Markers of Prognosis in Neurodegenerative Dementia

Stubendorff, Kajsa

2014

[Link to publication](#)

Total number of authors:
1

Markers of Prognosis in Neurodegenerative Dementia

Kajsa Stubendorff, MD

LUND UNIVERSITY
Faculty of Medicine

DOCTORAL DISSERTATION

With due permission of the Faculty of Medicine at Lund University to be publicly defended on May 9, 2014 at 9:00 am, in Lilla aulan, Jan Waldenströms gata 5, Skåne University Hospital, Malmö, Sweden

Faculty Opponent
Agneta Nordberg, Professor
Karolinska Institutet
Division of Translational Alzheimer Neurobiology,
Department of Neurobiology, Care Sciences and Society,
Stockholm, Sweden

Primary Supervisor
Elisabet Londos, Ass. Prof
Lund University

Assistant Supervisor
Lennart Minthon, Prof.
Lund University

Examination Board
Louise Bennet, Ass. Prof.
Lund University

Geir Selbaek, PhD
Oslo University Hospital

Michelle Chew, Ass. Prof.
Lund University

Organization	Document name
LUND UNIVERSITY	DOCTORAL DISSERTATION
Clinical Memory Research Unit	Date of issue
Department of Clinical Sciences, Malmö	May 9, 2014
Faculty of Medicine	
Author(s)	Sponsoring organization
Kajsa Stubendorff	

Title and subtitle
Markers of Prognosis in Neurodegenerative Dementia

Abstract

Background: A prognostic marker should provide information about course and outcome of disease, e.g. predict time to a given endpoint or rate of progression due to disease in patients or subgroups of patients. Prognostic markers could be targeted to apply during the entire clinical course or just during distinct stages of the disease.

Aim: The aim of this thesis is to identify, review and qualify possible indicators, including biological markers to predict course and time of survival in the two most common types of neurodegenerative dementia; AD and DLB/PDD.

Study populations:

I. 142 patients with AD.
II. 79 patients with AD and 49 patients with DLB.
III. 30 patients with DLB/PDD.
IV. 32 patients with DLB PDD.

Results:

I. Patients with very high T-tau levels performed worse on cognitive tests at baseline, and exhibited a more rapid cognitive decline during follow up. Very high T-tau levels were also associated with a deviating cognitive profile characterized by symptoms from the medial temporal lobes.

II. Patients with DLB had shorter length-of-survival compared to patients with AD, from the time of diagnosis, from the time of MMSE 20±1 and from the time of MMSE 17±1.

III. Patients with persistent orthostatic hypotension exhibited shorter length-of-survival compared to patients with no or mild orthostatic hypotension. Patients with constipation and / or urinary incontinence, in addition to persistent orthostatic hypotension, had the shortest survival.

IV. Patients, who received memantine instead of placebo during the first 6 months of follow-up, had a longer length-of-survival. Patients, who responded positively to memantine lived longer compared to the non-responders.

Conclusions: This thesis adds to current knowledge by reporting on studies on potential biomarkers that predict more rapid deterioration or shorter length-of-survival in neurodegenerative dementia. However, our findings must be confirmed in future research with larger study samples.

Key words
Alzheimer's disease, Lewy body disease, dementia with Lewy bodies, prognosis, survival, longitudinal studies, biomarkers, cerebrospinal fluid, dysautonomic orthostatic hypotension, memantine

Classification system and/or index terms (if any)

Supplementary bibliographical information	Language
	English

Recipient´s notes	Number of pages	Price
	142	
	Security classification	

Distribution by (name and address)

Signature _Kajsa Stubendorff_   Date _2014-03-25_

Markers of Prognosis in Neurodegenerative Dementia

Kajsa Stubendorff, MD

Clinical Memory Research Unit
Department of Clinical Sciences, Malmö
Faculty of Medicine
Lund University

Table of Contents

Abstract

Markers of Prognosis in Neurodegenerative Dementia

Background

A prognostic marker should provide information about course and outcome of disease, e.g. predict time to a given endpoint or rate of progression due to disease in patients or subgroups of patients. Prognostic markers could be targeted to apply during the entire clinical course or just during distinct stages of the disease.

Aim

The aim of this thesis is to identify, review and qualify possible indicators, including biological markers to predict course and time of survival in the two most common types of neurodegenerative dementia; AD and DLB/PDD.

Study populations

I   142 patients with AD.
II   79 patients with AD and 49 patients with DLB.
III   30 patients with DLB/PDD.
IV   32 patients with DLB PDD.

Results

I.   Patients with very high T-tau levels performed worse on cognitive tests at baseline, and exhibited a more rapid cognitive decline during follow up. Very high T-tau levels were also associated with a deviating cognitive profile characterized by symptoms from the medial temporal lobes.

II. Patients with DLB had shorter length-of-survival compared to patients with AD, from the time of diagnosis, from the time of MMSE 20±1 and from the time of MMSE 17±1.

III. Patients with persistent orthostatic hypotension exhibited shorter length-of-survival compared to patients with no or mild orthostatic hypotension. Patients with constipation and/or urinary incontinence, in addition to persistent orthostatic hypotension, had the shortest survival.

IV. Patients, who received memantine instead of placebo during the first 6 months of follow-up, had a longer length-of survival. Patients, who responded positively to memantine lived longer compared to the non-responders.

Conclusions

This thesis adds to current knowledge by reporting on studies on potential biomarkers that predict more rapid deterioration or shorter length-of-survival in neurodegenerative dementia. However, our findings must be confirmed in future research with larger study samples.

Sammanfattning på Svenska

De två vanligaste typerna av neurodegenerativ demenssjukdom är Alzheimer's sjukdom och Lewy body demens. Båda sjukdomarna drabbar framförallt äldre människor och risken att insjukna ökar med stigande ålder. Detta innebär att demenssjukdom kommer att bli vanligare i samhället, eftersom vi blir allt äldre och andelen invånare >65 år blir allt större. Att drabbas av demens innebär ett stort lidande för individen och dess anhöriga. Gemensamt för Alzheimer's sjukdom och Lewy body demens är att symtomen kommer smygande och tilltar successivt över tid. Symtombilden skiljer sig då Alzheimer's sjukdom i typfallet debuterar med minnesbesvär, medan Lewy body demens oftast börjar med försämrad rumsuppfattning, påverkan på vakenhet och uppmärksamhet eller hallucinatoriska upplevelser. Nedsatt minne kan tillkomma i senare stadier av sjukdomen.

Hur snabbt demenssjukdomen fortskrider skiljer sig mycket från individ till individ och vi saknar kunskap om hur vi kan förutsäga vem som drabbas av en aggressiv sjukdom och vem som försämras långsammare. Det gör det svårt för oss att sätta upp delmål och att ta medicinska beslut i rätt tid. Om vi skulle lära oss att förutsäga prognosen skulle vi bättre kunna svara på patienters och anhörigas frågor. De skulle bättre kunna förebereda sig för framtiden. Vårdpersonal och kommunala instanser skulle lättare kunna planera för kommande hjälpbehov och medicinering. Osäkerheten som föreligger nu, kring t ex förväntad överlevnadstid, leder till att demens inte hanteras som en terminal sjukdom och det blir i sin tur en barriär för att erbjuda svårt demenssjuka patienter en högkvalitativ vård i livets slutskede.

I vår kliniska vardag används ofta biomarkörer för att mäta biologiska processer eller tillstånd. Markörer kan förutsäga risk att utveckla sjukdom, sk *trait markers*. Diagnostiska markörer kallas *state markers*. *Stage markers* ger information om hur långt en sjukdomsprocess har progredierat. *Rate markers* kan användas som mått på sjukdomens intensitet och kan därför indirekt användas för att förutsäga prognosen. Mitt forskningsprojekt handlar om att försöka hitta prognosmarkörer vid demenssjukdom. Dessa prognosmarkörer bör kunna förutsäga överlevnad eller hur snabbt symtomen förvärras under sjukdomsförloppet.

Vid Minneskliniken i Malmö följer man patienter i strukturerade uppföljnings-program. Genom åren har man samlat in stora, prospektiva patientmaterial för longitudinella studier. I mina studier använder jag mig av olika delar av dessa material och jag har inriktat mig på diagnosgrupperna Alzheimer's sjukdom, Lewy body demens och Parkinsons sjukdom med demens.

Resultatet i mitt första arbete (Paper I) indikerar att man med hjälp av markören total-tau i ryggvätska (cerebrospinalvätska) kan förutsäga prognosen vid Alzheimers sjukdom. I arbete nr 2 (Paper II) fann jag att patienter med Lewy body demens har kortare överlevnad jämfört med patienter med Alzheimer's sjukdom, om man mäter från tiden då de får diagnos och från den tidpunkt då de presterar 17 eller 20 poäng på Mini-Mental test (MMT). I mitt tredje arbete (Paper III) visar jag att förekomst av svår autonom dysfunktion troligen är associerad med kortare överlevnad hos patienter med Lewy body demens och vid Parkinsons sjukdom med demens. I mitt fjärde arbete (Paper IV) talar resultaten för att behandling med Memantine och behandlingsrespons, har betydelse för överlevnaden hos patienter med Lewy body demens och Parkinsons sjukdom med demens.

Jag har alltså funnit att etablerade kliniska variabler som T-tau i cerebrospinal-vätska, typ av demens, autonom dysfunktion och svar på läkemedelsbehandling möjligen även kan användas som prognosmarkörer vid neurodegenerativa sjukdo-mar. Mina studiepopulationer är små och fynden måste bekräftas i större studier innan man kan tillämpa dem kliniskt.

Thesis at a Glance

Objectives	Setting	Study design	Main results	What did I learn?
Do very high levels of T-tau correlate with more rapid cognitive decline or a different cognitive profile on MMSE in AD?	Baseline CSF biomarkers and repeated cognitive testing during 3 years follow-up. Diagnosis: AD	Longitudinal Prospective	Patients with high T-tau levels performed worse on cognitive tests at baseline, had a different cognitive profile, and exhibited a more rapid cognitive decline during the follow-up	The basics of SPSS. The neurochemistry of Alzheimer's disease. How to write a scientific article.
Does type of dementia influence prognosis?	Assessment of survival-length from selected time-points during 5-10 years clinical follow-up. Diagnosis: AD and DLB	Longitudinal Prospective	Patients with DLB had a shorter length-of-survival compared to patients with AD, from the time of diagnosis, from the time of MMSE 20±1 and from the time of MMSE 17±1.	Scientific methods to investigate differences in survival and prognosis and their limitations. Survival analysis.
Is autonomous dysfunction associated to a shorter survival in DLB/PDD?	Baseline survey of dysautonomic symptoms and repeated blood pressure measurements during 3 years follow-up Diagnosis: DLB/PDD	Longitudinal Prospective	Patients with persistent orthostatic hypotension exhibited shorter length-of-survival compared to patients with no or only mild orthostatic hypotension.	Scientific methods to evaluate autonomous dysfunction, primarily orthostatic hypotension.
Can treatment effect serve as a prognostic marker? Does Memantine influence survival in DLB/PDD?	Evaluation of treatment effect 24 weeks after baseline and assessment of survival-length during the 3 years follow-up Diagnosis: DLB/PDD	Longitudinal Prospective Double-blinded placebo-controlled (week 0–24)	Patients who received memantine instead of placebo had a longer length-of-survival. Patients who responded positively to memantine lived longer compared to the non-responders.	Scientific methods to evaluate treatment effect.

Abbreviations

Aß	ß-amyloid
AD	Alzheimer's disease
ADAS-cog	Alzheimer Disease Assessment Scale – Cognitive Subscale
ADL	Activities of Daily Living
APOE	apolipoprotein E
CGIC	Clinical Global Impression of Change
ChEI	cholinesterase inhibitors
CSF	cerebrospinal fluid
CT	computed tomography
CVL	cerebrovascular lesion
DAD	Disability Assessment of Dementia
DLB	Dementia with Lewy Bodies
DSM-IV	Diagnostic and Statistical Manual of Mental Disorder – 4th revision
EPS	extrapyramidal symptoms
ICD-10	International Classification of Disease – 10th revision
MAS	Malmö Alzheimer Study
MCI	mild cognitive impairment
MEMDLBPDD	The Memantine Study
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NCD	neurocognitive disorder

NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NMDA	N-methyl D-aspartate
NPI	Neuropsychiatric Inventory
PD	Parkinson's disease
PDD	Parkinson's disease with Dementia
PET	positron emission tomography
P-tau	phosphorylated tau
RCT	randomized controlled study
RBD	REM sleep behavioral disturbance
SATS	Swedish Alzheimer Treatment Study
SPSS	Statistical Package for Social Sciences
T-tau	total tau
UPDRS	Unified Parkinson's Disease Rating Scale
VaD	vascular dementia

List of Publications

The thesis is based on the following four papers, referred to in the text by their Roman numerals.

Paper I

Sämgård K, Zetterberg H, Blennow K, Hansson O, Minthon L, Londos E. *Cerebrospinal fluid total tau as a marker of Alzheimer's disease intensity* Int J Geriatr Psychiatry. 2010 Apr;25(4):403-10. doi: 10.1002/gps.2353

Paper II

Stubendorff K, Hansson O, Minthon L, Londos E. *Differences in Survival between Patients with Dementia with Lewy Bodies and Patients with Alzheimer's Disease – Measured from a Fixed Cognitive Level.* Dement Geriatr Cogn Disord. 2011;32(6):408-16. doi: 10.1159/000335364. Epub 2012 Feb 8

Paper III

Stubendorff K, Aarsland D, Minthon L, Londos E. *The impact of autonomic dysfunction on survival in patients with dementia with Lewy bodies and Parkinson's disease with dementia* PLoS One. 2012;7(10):e45451. doi: 10.1371/journal.pone.0045451. Epub 2012 Oct 1.

Paper IV

Stubendorff K, Larsson V, Ballard C, Minthon L, Aarsland D, Londos E. *Treatment Effect of Memantine on Survival in DLB and PDD: a prospective, 3 year follow-up study.* Submitted to BMJ Open 2014-02-28

Paper I and Paper II are reproduced with permission from John Wiley and Sons and Karger publishers respectively.

In July 2011, I married Johann Stubendorff. My family name was then changed from Sämgård to Stubendorff.

1. Introduction

1.1. Dementia

The 10th revision of the International Classification of Disease (ICD-10)[1] was endorsed by the World Health Organization (WHO) in 1990 in order to establish a global health standard for morbidity and mortality statistics. The general definition of dementia is "progressive disabling mental impairment", while ICD-10 criteria for dementia include: deterioration in memory severe enough to impair social functioning and impairment in performing activities of daily living (ADL). Memory impairment includes deficits in registration, storage and retrieval of new information, and there should also be a decline in other cognitive abilities characterized by deterioration in judgments and thinking, such as planning and organizing, and in the general processing of information. Symptoms must have been present for at least 6 months.

The American Psychiatric Association's fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [2], provides criteria for the diagnosis of dementia that include memory disturbance and impairment in at least one additional cognitive function (aphasia, apraxia, agnosia or executive function). The change from previous higher levels of function must be significant and deficits must affect occupational or social function.

According to both the DSM-IV and ICD-10 the diagnosis of dementia is based on clinical symptoms, regardless of underlying biological events. Hence, the condition can be caused by several different disorders.

In June 2013, the latest DSM, the Fifth edition (DSM-5), was released [3], which includes substantial changes in the nomenclature. The term "neurocognitive disorders" (NCD) was added and "dementia" eliminated. Neurocognitive disorders were separated into minor or major. In this scheme cognitive and functional deficits are equivalent to both the major NCD and in former dementia. However, mild NCD is treated uniquely, in that, only "modest cognitive decline from previous level" is required and cognitive deficits do not necessarily have to interfere with independence, though the individual may be required to use greater effort, compensatory strategies, or to accommodate to maintain independence. The introduction of mild NCD is a significant change that is in line with the interest in establishing diagnoses earlier in the disease process, which is made possible by technical improvements to

early diagnostication [4,5]. Note that the old terminology required the presence of memory impairment. However, it has been recognized that, in a number of brain diseases leading to cognitive impairment, memory is not the first domain to be affected. Consistently, DSM 5 also includes complex attention, executive function, language, perceptual motor problems and social cognition among the neurocognitive domains that can be impaired by an NCD [4].

1.2. Alzheimer's disease

Diagnostic criteria

In the DSM-IV, the diagnosis of Alzheimer's disease (AD) must meet the criteria for dementia of gradual onset and progressive decline of symptoms, but it is also an exclusionary diagnosis. Other causes of dementia (e.g. cerebrovascular disease, Parkinson's disease, Huntington's disease, systemic diseases and drug induced conditions) must be ruled out.

In the new DSM-5 criteria [3], after typing cognitive ability as normal versus mild or major NCD, an etiological category is determined, such as mild or major NCD due to AD.

The most widely used diagnostic criteria in research on AD were established in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[6] (Table 1). In this manual, dementia symptoms must be confirmed by neuropsychological testing. Imaging and laboratory tests are important to exclude other possible conditions. Diagnosis of AD is then made as probable, possible or definite, where the diagnosis of definite AD can only be obtained after histopathologic postmortem examination.

Table 1. The NINCDS –ADRDA criteria for clinical diagnosis of Alzheimer's disease [6]

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:
• dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale,' or some similar examination, and confirmed by neuropsychological tests; • deficits in two or more areas of cognition; • progressive worsening of memory and other cognitive functions; • no disturbance of consciousness; • onset between ages 40 and 90, most often after age 65; and • absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease is supported by: • progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia); • impaired activities of daily living and altered patterns of behavior; • family history of similar disorders, particularly if confirmed neuropathologically; and • laboratory results of: normal lumbar puncture as evaluated by standard techniques, normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and evidence of cerebral atrophy on CT with progression documented by serial observation.
III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include: • plateaus in the course of progression of the illness; • associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss; • other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder; • seizures in advanced disease; and • CT normal for age.
IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include: • sudden, apoplectic onset; • focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and • seizures or gait disturbances at the onset or very early in the course of the illness.
V. Clinical diagnosis of POSSIBLE Alzheimer's disease: • may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course; • may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be *the* cause of the dementia; and • should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.
VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are: • the clinical criteria for probable Alzheimer's disease and • histopathologic evidence obtained from a biopsy or autopsy.
VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as: • familial occurrence; • onset before age of 65*;* • presence of trisomy-21; and • coexistence of other relevant conditions such as Parkinson's disease.

The NINCDS-ADRDA criteria from 1984 demonstrate good reliability and validity when compared with postmortem diagnoses [7] and are diagnostically accurate to 65%-96% [8,9,10,11,12,13].

Since the publication of those NINCDS-ADRDA criteria the scientific knowledge regarding the neuropathological features of AD has greatly expanded. This, together with new technical methods (e.g. identification of cerebrospinal fluid biomarkers and imaging methods), makes it possible to characterize the phenotypic basis for AD and, consequently, clinical AD needs no longer to be described in exclu-

sionary terms. Furthermore, the ability to recognize and define non-AD dementias has improved. This leads to investigators to consider new criteria for diagnosing AD.

The Dubois criteria [14] were published in 2007 and they suggest that at least one or more abnormal biomarker must be present from among the following: structural neuroimaging with magnetic resonance imaging (MRI), molecular neuroimaging with positron emission tomography (PET) and cerebrospinal fluid (CSF) analysis of amyloid and tau proteins.

In 2011, the National Institute on Aging (NIA) and the Alzheimer Association revised the NINCDS-ADRDA criteria [15], including incorporating biomarkers of underlying disease states and formalizing three different phases of Alzheimer's disease; dementia phase (AD dementia), symptomatic pre-dementia phase (Mild cognitive impairment (MCI)) and asymptomatic preclinical phase (preclinical AD) The rationale behind these were, in part, that correspondence about clinical versus pathological findings were not easily comparable. Indeed, AD pathology was at times present even in the absence of frank dementia symptoms. The revised criteria separated the findings based on underlying pathological process from those findings based on clinical examination. Thus, it is possible to obtain an AD diagnosis even in the absence of dementia (preclinical AD). It had also been shown that the onset of neuropathological changes precedes dementia symptoms by decades. This preclinical phase potentially provides an opportunity for therapeutic intervention. The recommendations regarding AD dementia [16] and MCI due to AD [17] are intended for clinical settings, but the recommendations of the preclinical AD are intended purely for research purposes [18].

Pathogenesis of AD

In 1906, Professor Alois Alzheimer lectured "On a Peculiar, Severe Disease Process of the Cerebral Cortex", on the case of Auguste Dieter. He had examined this woman when she, at the age of 51, had developed progressive memory disturbances. After her death, Alzheimer's postmortem examination revealed that the cerebral cortex was thinner than normal and that miliary bodies (plaques) and dense bundles of fibrils (tangles) were present [19].

Amyloid plaques and neurofibrillary tangles are histologic hallmarks of AD. It is clear today, however, that such lesions are also found on examination of otherwise healthy elderly [20]. The pathological process starts probably decades before clinical symptoms appear [21,22]. Neurodegeneration is typically most pronounced in hippocampal regions [23], but in severe AD, evidence shows general brain atrophy and widened sulci and ventricles.

Plaques are extracellular aggregates of amyloid ß (Aß) peptide. The Aß peptide is cleaved from the amyloid precursor protein (APP) and is produced constitutively during normal cell-metabolism [24]. The amyloid-cascade hypothesis has been the preponderant theory for the cause of Alzheimer's disease for more than 20 years, yet

it is not fully understood why the deposits emerge in AD. An imbalance between production and clearance of Aß in the brain is thought to be the initiating event leading to AD [25]. Aß 40 and Aß 42, named according to cleavage site, have been the most investigated. The latter is the most prone to conform into a ß-sheet structure and it also triggers the misfolding of other Aß species. They form soluble oligomers that eventually aggregate into insoluble fibrils, generating plaques [26,27,28]. For many years, the Aß plaques were thought to be neurotoxic, but more recent findings suggest that the soluble oligomers are the culprits that harm synaptic plasticity, leading to neurotransmitter deficits and by extension, synaptic degeneration and neuronal death [29,30].

A parallel hypothesis is that tau protein metabolism abnormalities trigger AD pathogenesis. Tau is a normal intracellular protein that binds to and stabilizes microtubules [30]. In AD, unexplained hyperphosphorylation of the tau protein leads to destabilization of the microtubule system, and subsequently to axonal dysfunction and eventual neuronal death [31]. Hyperphosphorylated tau also tends to form intracellular neurofibrillary tangles [30]. These first appear in the entorhinal cortex. However, these proliferate with disease progression and are later observed to accumulate in temporal regions (hippocampus, amygdala) as well as in parietal and frontal cortex [32,33]. Even though Aß deposits have been found to increase with disease severity [34], a recent review reported that the severity of cognitive impairment more highly correlates with the burden of neocortical neurofibrillary tangles than Aß deposits [35].

Beside the amyloid and tau hypotheses, additional possible mechanisms have been explored, including those associated with inflammatory processes, cerebrovascular disease, oxidative stress, mitochondrial dysfunction and synaptic dysfunction. Evidence suggests converging pathogenic mechanisms [30,36,37].

Therapeutic approaches

Current therapeutic approaches to Alzheimer's disease are addressed to its symptoms. Despite our greater understanding about neurodegeneration, including molecular pathways and mechanisms, no disease modifying therapy is available.

The "cholinergic hypothesis" evolved during the 1970s, when Bowen et al. first described reduced choline transferase activity in the cerebral cortex of AD patients [38]. This finding indicated a downstream effect associated with selective neuronal loss in the nucleus basalis of Meynert (basal forebrain) [39] leading to cholinergic deficits in the hippocampus and neocortex, which are important regions for memory and learning . This was the rationale behind the development of cholinergic pharmacotherapies. Today, cholinesterase inhibitors (ChEIs), including donepezil, rivastigmine and galantamine, are approved for clinical use in AD. These delay the breakdown of acetylcholine being released into synaptic clefts, and so enhance cholinergic neurotransmission. The most recent of the Cochrane Reviews, concluded that all three are efficacious in mild-to-moderate AD [40], and ChEIs

are undoubtedly the first line of pharmacotherapy in AD. Memantine is the only non-cholinergic treatment approved for AD. In vitro and in animal models, it is noted that Aß plaques increase the neuron's vulnerability to excitotoxicity [41,42], i.e. excessive expression of the neurotransmitter glutamate and over-activation of N-methyl-D-aspartate (NMDA) glutamate receptors, leading to neuronal injury or death [43]. Being a low affinity antagonist to NMDA receptors, memantine is believed to prevent excitotoxic neuronal death [43,44]. A Cochrane Review from 2005 obtained data that suggests a small beneficial effect of memantine in moderate-to-severe stages of AD, while the effect in mild AD remains unknown [45].

Substantial effort has been made to find the ultimate goal: A therapy which impacts the disease process in a fundamental way. Major strategies have included inhibiting Aß production and its aggregation in the brain, and increasing Aß clearance through immunization. Results from investigations using animal models have been promising, though none of these approaches have shown sufficient disease-modifying effect in phase III studies on humans, and there have been serious side-effects. If a disease-modifying treatment for AD is found, it will most likely have its greatest effect when administered early in disease [46]

1.3. Dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD)

Diagnostic criteria

In Japan 1984, Kosaka and colleagues proposed that "diffuse Lewy Body disease" (DLBD) is a disease entity [47], and their theories were based on case reports. In England, some years later, Perry and colleagues described the equivalent "senile dementia of Lewy body type" (SDLT) [48]. In 1990, Hansen et al. reported from USA, that 33% of their cases with AD pathology also had Lewy body pathology [49]. They referred to these cases as "Lewy body variant" of AD (LBV). In 1995, a consensus was reached that DLBD, SDLT and LBvAD represent the same diagnostic entity, and so, the first diagnostic consensus criteria for DLB were established [50]. These criteria enable a clinical diagnosis of probable or possible DLB, while definite diagnosis can be obtained only from postmortem examination of the brain.

The consensus criteria further classify according to *central, core* and *supportive features*. The central feature for the diagnosis of DLB is dementia. To obtain the *probable* DLB diagnosis dementia must be accompanied by two core features, including fluctuating cognition, visual hallucinations or parkinsonism. A *possible* diagnosis of DLB requires dementia and one core feature together with at least one supportive feature (repeated falls, syncope, transient loss of consciousness, neuroleptic hypersensitivity, systematized delusions or hallucinations in other modalities). Evaluation of these criteria has shown acceptable specificity, but low sensitivity [51,52].

With the aim to ameliorate the diagnostic sensitivity, revised consensus criteria were published in 2005 (Table 2) [53]. Apart from the *central* and *core* features, clinical features that are *suggestive* (significantly more frequent in DLB compared to other dementing disorders) are distinguished from *supportive* (commonly occurring, but not specific) when making the diagnosis. In research, DLB and Parkinson's disease with dementia (PDD) are seen as the same entity, as outlined in the consensus criteria below, but a distinction between the two is made based on the time of onset of cognitive and motor symptoms.

Table 2. Revised criteria for the clinical diagnosis of DLB [53]

Central feature (essential for a diagnosis of probable or possible DLB)
Dementia defined as progressive disabling cognitive decline. Prominent or persistent memory impairment may not necessarily occur in early stages but is usually evident with progression.
Core features (two core features are sufficient for probable DLB, one for possible DLB)
• Fluctuating cognition with pronounced variations in attention and alertness. • Recurrent visual hallucinations are typically well formed and detailed • Spontaneous features of Parkinsonism
Suggestive features (A diagnosis of probable DLB requires one or more suggestive feature in the presence of one or more core features. In the absence of any core features, one or more suggestive features are sufficient for possible DLB.)
• REM sleep behavior disorder • Severe neuroleptic sensitivity • Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging.
Supportive features (not proven to have diagnostic specificity)
• Repeated falls and syncope • Transient, unexplained loss of consciousness • Severe autonomic dysfunction e.g. orthostatic hypotension, urinairy incontinence • Hallucinations in other modalities • Systematized delusions • Depression • Relative preservation of medial temporal lobe structures on CT/MRI scan • Generalized low uptake on SPECT/PET perfusion scan, with reduced occipital activity • Abnormal (low uptake) MIBG myocardial scintigraphy • Prominent slow wave activity on EEG with temporal lobe transient sharp waves
A diagnosis of DLB is less likely
• In the presence of cerebrovascular disease evident as focal neurologic signs on brain imaging • In the presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture. • If Parkinsonism only appears for the first time at a stage of severe dementia
Temporal sequence of symptoms
DLB should be diagnosed when dementia occurs before or concurrently with Parkinsonism (if it is present). The term Parkinson disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as LB disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD the existing 1-year rule between the onset of dementia and Parkinsonism DLB continues to be recommended. Adoption of other time periods will simply confound data pooling or comparison between studies. In other research settings that may include clinicopathologic studies and clinical trials, both clinical phenotypes may be considered collectively under categories such as LB disease or alpha-synucleinopathy.

Pathogenesis of DLB and PDD

The neuropathological features of Lewy body disease had been described much earlier than the dementing disease. In 1912, Dr. Frederich Henry Lewy, who had studied patients with Parkinson's disease (PD), described intraneuronal inclusions in the dorsal vagal nucleus and nucleus basalis of Meynert. These inclusions are still today the histological hallmark of Lewy body disease (including PD, DLB and PDD) [54]. In 1919, Dr Trietiakoff noted that these inclusions were mainly located in the substantia nigra and he called them "corps de Lewy" [55]. Later, Dr. Lewy also noticed widespread cortical distribution of such Lewy bodies in patients with Parkinson's disease, but he did not seem to pay much attention to these findings. Perhaps, he neither realized the huge significance of the Lewy bodies in the pathogenesis of PD nor their connection to dementia [56].

Today we know that Lewy bodies do occur in the central and peripheral nervous system, as well as in the autonomous nervous system [57,58,59]. We also know that Lewy bodies and the more recently described Lewy neurites consist of pathologic aggregates of α-synuclein, which normally is a presynaptic protein involved in vesicle production [52]. In the group of disorders called synucleinopathies, i.e. PD, PDD, DLB and multiple system atrophy (MSA) [60], pathological upregulation of α-synuclein production or genetic factors may lead to an increased tendency by α-synuclein to misfold and aggregate [61,62], but the exact trigger mechanisms are not known. Through several phases, α-synuclein forms oligomeric fibrils that aggregate into insoluble filamentous intracellular inclusions [58]. Recommended DLB diagnostic criteria call for semi-quantitative grading of lesion density in brainstem, limbic area, and five cortical regions, distinguishing three different phenotypes – brainstem-predominant, limbic, or diffuse neocortical [53]. Cortical Lewy bodies and Lewy neurites are widespread findings in DLB and PDD cases, and have been found to correlate with dementia severity [63,64,65]. Cortical Lewy bodies are equally distributed in DLB and PDD [66], excepting tissue from the temporal lobes where the Lewy body density is higher in DLB. A study of the symptoms and pathology of 100 patients with PD reported that cortical Lewy bodies occurred in all cases, though only four patients fulfilled the criteria for diffuse Lewy body disease [67]. The Braak hypothesis posits a temporal progression beginning when the Lewy bodies first appear in the pons and brain stem, and then propagating via the forebrain and limbic system to the neocortex [68]. The typical, well-formed visual hallucinations in DLB are associated with findings of increased number of Lewy bodies in the anterior and inferior temporal lobe [69], and autonomic dysfunction in DLB and PDD is thought to be associated with the presence of Lewy bodies in autonomic ganglia and autonomic brain stem nuclei [70]. In general, however, weak correlations are found among clinical symptoms, disease duration and Lewy body density [71]. This suggests that DLB should not be considered just at severe form of PD. The significance of Lewy body pathology in neurodegeneration and what relationship it has to clinical signs and symptoms must be further elucidated [58].

Studies suggest that Lewy neurites and neurotransmitter deficits may better correlate with clinical symptoms [71,72].

In addition to Lewy body pathology, most patients with DLB have concomitant AD pathology, as the number of amyloid plaques is equivalent to that in AD [73]. Disease duration as well as level of dementia severity are related to both Lewy body density and the grade of amyloid plaques, suggesting that dual pathologies cause DLB [66]. Neurofibrillary tangles occur to a lesser extent compared to in AD [52] and it has been reported that DLB patients with more tangles show a more AD-like pattern [74,75]. Coexisting AD pathology is less frequent in PDD [73,76,77]. Cortical and hippocampal atrophy is more limited in DLB compared to AD [78] and even more limited in PDD compared to DLB [73].

Therapeutic approaches

Up to now no treatment is available to modify the course of disease in DLB and PDD. The current therapeutic approach is, therefore, targeted toward symptoms, including cognitive impairment, neuropsychiatric symptoms, visual hallucinations, parkinsonism and various functional deficits. The pharmacological targets aim to modify abnormal levels of neurotransmitter or other neurochemicals following neuronal degeneration in selected areas of the brain.

The cholinergic nucleus basalis is a site of predilection for Lewy bodies and deficits in cortical cholinergic activity are well known in both DLB and PDD [79], and even more severe than in AD [80]. Also, decreased performance on cognitive tests correlates with cortical cholinergic denervation in PD and PDD [81] and this is the rationale for treatment with choline esterase inhibitors in DLB and PDD. A recent Cochrane analysis concluded that cholinesterase inhibitors positively impact global assessment, cognitive function, behavioral disturbance and activities of daily living in PDD. The evidence for treatment efficacy using choline esterase inhibitors in DLB is weaker [82]; and, currently, rivastigmine is the only therapy licensed for treatment of cognitive impairment in PDD. A study from 2004, found abnormal glutamate receptor expression and signaling in cortical areas in DLB patients, and hypothesized that abnormal α-synuclein in DLB produces functional effects on cortical glutamatergic synapses [83]. Thus, memantine may be beneficial also in DLB/PDD patients [79], with the same molecular mechanisms of action as described for AD (see page 22). Two of four randomized, placebo-controlled trials (RCTs) investigating the effect of memantine on cognition in PDD [84,85,86,87] also included DLB patients [84,85]. Memantine was well-tolerated and all studies found positive effects from treatment, but consistent benefits across the studies are only evident on global outcome. Follow- up studies on the Swedish cohort of the Aarsland study [84] found additional benefits both in treatment of sleep disturbances [88] and in improvement in quality of life [89]. Dopaminergic changes in DLB and PDD, following neuronal loss in the substantia nigra account for motor deficits. Levodopa

is the drug of choice in PD, but should be used with caution in DLB and PDD. In PDD, high doses can cause cognitive deterioration [90] and its adverse effects in DLB include visual hallucinations and sleep disturbances [91]. Antipsychotics should be avoided because of the specific risk for adverse advents and severe neuro-leptic sensitivity in DLB and PDD patients [79]. Neuropsychiatric symptoms and visual hallucinations may therefor present a clinical dilemma in these patients.

1.4. Epidemiology

A meta-analytic study on the prevalence of dementia worldwide was published in 2013 [92]. Study authors, Prince et al., estimated that 35.6 million people in the world live with dementia. However, due to population growth and demographic aging, the total number of people with dementia is expected to nearly double every 20 years, to 65.7 million by 2030 and 115.4 million by 2050. In most regions the prevalence lies between 5%-7% in the group aged >60. Currently, Western Europe is the region with the largest number of people with dementia (7.0 million), but compared to less developed regions of the world, only a moderate proportionate increase is expected. According to statistics from the Swedish National Board of Health and Welfare [93], approximately 142, 000 individuals live with dementia in Sweden and every year, 25, 000 new individuals will become afflicted. In Sweden, the prevalence in individuals aged 60-64 years is 1% and about 25% in people 85-89 years old.

Most commonly diagnosed of the neurodegenerative dementing disorders is AD, which accounts for 50-60% of all cases [30]. The second most common neurode-generative dementia is DLB and PDD occurring in 15-20% and 3-4% of all de-mentia cases, respectively [62,94,95].

1.5. Risk factors for dementia

There are genetic risk factors, where the isoform ε4 of apolipoprotein E (APOE) is the most well-established risk factor for sporadic and familial AD [96]. Individuals with one ε4 allele are 2-5 times more likely to develop AD and the genotype ε4/ε4 5-to 10- fold increase in risk or more [97]. Age is an obvious risk factor for dementia as incidence increase almost exponential with age, but it is important to look at risk factors that become more likely as we age. Elevated systolic blood pressure, especially in midlife, is one of many modifiable risk factors in AD and in all-cause dementia [98,99]. However, also low diastolic pressure [98] and decline in blood pressure levels over time [100,101] have been found to increase the risk of

dementia. Midlife elevated serum cholesterol increases the risk for dementia in later life [102,103]. Smoking increases the risk for dementia [104,105], whereas small amounts of alcohol have been found to be protective [106]. Several lifestyle factors have been reported to reduce the risk of dementia, including engaging in physical activity [105,107], and to a lesser extent, "social engagement" and "cognitive stimulation" [107]. Dietary factors have been extensively studied as possible modifiable risk factors, but there is a lack of RCTs and few studies reported conclusive findings [107]. A review from 2007 states, however, that high fat intake increases dementia risk, while regular intake of fish and seafood appears to be protective [105].

1.6. Dementia in society

The total worldwide cost of dementia was estimated to be $422 billion (≈323 billion EURO) in 2009 [108]. In 2005, the total cost of dementia in Sweden was estimated as 50 billion SEK (≈5,3 billion EURO). Of the 142, 000 individuals with dementia, approximately 64, 500 (45%) were estimated to live in residential settings [93].

1.7. Quality of life

Auguste Dieter was the first person to be diagnosed with Alzheimer's disease. In her medical records, Dr. Alois Alzheimer made notes of the conversations he had with her during the examinations. Once he told Auguste to write her name. She tried, but failed, instead repeated the words "Ich habe mich verloren" ("I have lost myself") [109]. The fear of losing oneself or losing control is common among individuals with dementia [110] and to cope with ones symptoms, disabilities, emotions and diminished sociality is a particular challenge. Personal consequences for patients with dementia and their families are however difficult to account. Many family members are unpaid caregivers producing so called informal care and they often suffer from physical, emotional, financial or social distress [111], which in health economic research often is referred to as "intangible costs" [93]. An increasing number of studies highlight quality of life as an important outcome measure in patients with dementia and their caregivers. Wagner et al. [112] describe the important role of the medical care system to provide the patients and their families with enough knowledge and self-confidence to manage their condition. Based on a Cochrane review of successful care of diabetes patients, Wagner et al. tried to pinpoint what characterizes effective chronic illness care. The interaction between the patient and the medical care team is central and should optimally

1. elicit and review data concerning patients' perspectives and other critical information about the course and management of the condition(s);
2. help patients to set goals and solve problems for improved self-management;
3. apply clinical and behavioral interventions that prevent complications and optimize disease control and patient well-being;
4. ensure continuous follow-up.

The professional team surrounding a person suffering from dementia has great possibilities to support the patient and family in many ways, but the lack of prognostic markers makes it difficult to communicate expectations about the course and to set realistic goals for the future.

2. The Clinical Course of Dementia and the Prerequisites for Research on Prognosis

2.1. The terminology of prognostic markers

A prognostic marker should provide information about course and outcome of disease, e.g. predict time to a given endpoint or rate of progression due to disease in patients or subgroups of patients. Prognostic markers could be targeted to apply during the entire clinical course or just during distinct stages of the disease.

In this thesis we use terminology proposed by Fox and Growdon [113], that the role of a biomarker is to specify state, rate or trait. A disease-*state marker* typically may serve as a diagnostic marker and should be judged to exhibit high specificity and sensitivity, and utility in clinical practice. A *rate marker* provides information on the intensity of disease progression. Practically, it could predict how quickly symptoms will worsen or be useful in assessing change due to treatment. The risk of Alzheimer disease is higher among those with APOE4, which is thereby a *trait marker*. Furthermore, a measure can be used to tell how far the disease process has proceeded, including for example assessment scores for cognitive performance, functional status or level of caregiver burden. We call these markers disease-*stage markers*.

FIGURE 1a-c: Schematic illustration of the different types of prognostic markers; state, stage and rate.
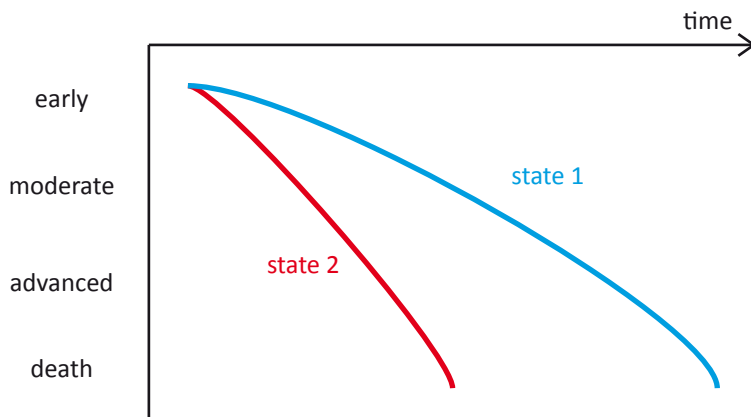
Figure 1a. A state marker is typically a diagnostic marker, responding to the question "disease yes or no". A state marker may similarly help to identify subgroups of patients within or beyond diagnostic groups.
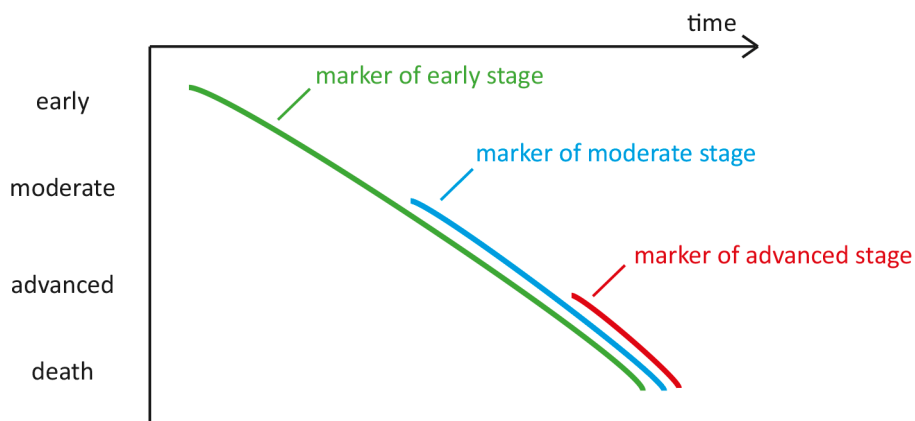
Figure 1b. Stage markers carry information on how far a patient has reached along the disease course. A stage marker indicates for example early or advanced disease stage, and can be still present as illustrated in this figure, or absent in the following (later) stages.
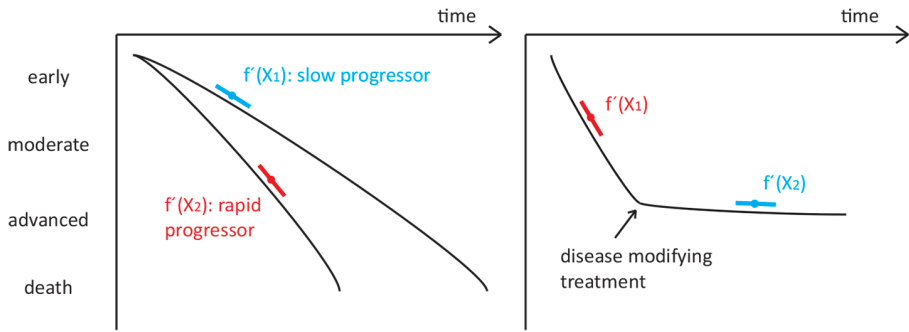
Figure 1c. Rate markers indicate the rate of progression through stages. It may tell how rapidly the disease progresses, and therefore inform prognosis. Rate markers are needed to detect true treatment effects from disease-modifying drugs, as illustrated in the right figure.

Our interpretation of this terminology is that state, stage, and rate markers may function as prognostic markers (Figure 1). A state marker can help to identify a subgroup of patients who encounter a particular quality of disease course. A stage marker can indicate how far a patient has progressed along the disease course and, therefore, estimate the proximity of final stages or death. A rate marker can indicate how rapidly the disease may progress, and thus informs us about the prognosis.

2.2. The spectrum of neurodegenerative diseases

2.2.1. The individual spectrum (recovery – deterioration)

An increasingly important concept in the care of elderly and in research on aging is frailty, which can be described as a biological syndrome of reduced reserve capacity and impaired resistance to stressors, causing vulnerability to adverse events [114]. Accordingly, a widely used definition proposed by Fried et al. is that a person is "frail" if three of the following are present: weight loss, exhaustion, weakness, slow walking speed and low levels of physical activity [115]. Frail patients have increased risk for falls, fractures, disability, institutionalization and death, probably resulting from accumulative decline across multiple physiologic systems [114,116]. Besides age-related physical changes, frailty-risk factors include inflammation [117], poly-pharmacy [118], nutritional factors [119], hormonal factors [120], cardiovascular disease [121] and psychosocial factors [122]. Several reports have addressed the relationship between dementia, cognitive decline and frailty, and there seem to be a strong clinical correlation [114]. In a recent study, Kulmala et al. found that frail

persons were 8 times more likely to have clinically diagnosed dementia compared to non-frail in a random sample of older people [123]. A study of autopsy concluded that frailty is associated with AD pathology, with and without dementia [124]. The etiopathogenesis is not clear, but dementia and frailty independently predict future adverse health events [114,116]. Hence, older persons with *both* cognitive impairment and frailty incur especially high-risk.

Delirium is another common condition in patients with dementia, leading to acute behavioral and psychological disturbances [see review, 125]. Even though delirium generally is a reversible condition, there is a known delay in diagnosis in demented patients [126] and symptoms are often blamed on the underlying dementing disease itself. Santangelo et al. found that the clinical complexity, including prevalence of concomitant delirium, is even higher in DLB patients compared to other dementing disorders [127]. Delirium may, especially if not recognized and managed properly, alter the clinical course and increase the rate of cognitive decline in dementing patients and thus severely degrade the prognosis [126].

The high prevalence and high cost of the comorbidity, frailty and delirium, are important reasons to perform long-term follow-up studies on patients with neurodegenerative dementia. At the same time, these conditions make such studies demanding, with high drop-out rates, leading to statistical limitations. Observed cognitive or functional deterioration during clinical follow up can be due to progress in the dementia disease itself, to fluctuations (in DLB or PDD) or to superimposed conditions affecting cognitive or functional ability. Deterioration could be temporary or permanent, making it hard to interpret changes over time, especially if data have been retrospectively collected. Some recommend longer inter-test intervals [128], others longer follow-up time (more than 1 year) [129], in order to establish a consistent pattern of disease progression.

2.2.2. The intra individual spectrum (slow progress – rapid progress)

Since the 1990s many studies have tried to describe the clinical course of dementia. The time of survival and the rate of progression have been shown to be highly variable between individual patients. In literature, the reported duration of disease in AD ranges from a few months to 21 years [130]. Great effort has been made to identify predictors of rapid and slow "progressors", but the definition of rapid progression has differed between studies [see review, 131], as have the outcome measures, statistical approaches, follow-up intervals and the total time of follow-up. Some research suggests that variation in the progression of decline can be shown as distinctly different models. Several distributions may be present, i.e. several distinct patterns of deterioration. If so, the different rates of progression might suggest different subgroups of AD, each with distinct and different pathophysiology. Interestingly, Thalhauser et al. mathematically analyzed longitudinal data obtained from 648 AD

patients that described their rate of progression and they found two separate distributions of progression [132]. The idea that multiple mechanisms may be in play, leading to clinical heterogeneity in AD, is also set out by Iqbal et al. whose analyses identified five subgroups of AD patients based on CSF levels of Aß42, T-tau and ubiquitin [133]. They also found that the pattern and prevalence of selected clinical symptoms (hallucination, hypokinesia, paranoia, rigidity, and tremors) varied from AD subgroup to subgroup [134].

2.2.3. The diagnostic spectrum (AD-DLB/PDD-PD)

Despite the diagnostic criteria, dementia syndromes may be difficult to distinguish. Atypical presentations and overlap among several common clinical features confound the diagnostic groups. Discrimination between diagnoses may be especially difficult early in the clinical course when symptoms are subtle, and in later stages as the progressive dysfunction leads to cumulative multiple deficits and greater overlap of symptoms across groups. Loss of episodic memory is typically more pronounced in AD compared to DLB, but this difference can be harder to recognize in later stages of DLB [52]. Extrapyramidal signs are key features in DLB but they also occur in advanced AD [135]. Alzheimer disease and DLB are probably most difficult to differentiate [136]. Recommendations are being made to remedy this, for example, including REM (rapid eye movement) sleep behavioral disorder (RBD) as a core clinical feature in DLB criteria [137], and establishing the presence of non-motor symptoms associated with PD (i.e. autonomic dysfunction), which have improved diagnostic accuracy [138]. The clinical overlap may reflect the underlying neuropathology where AD pathology and Lewy bodies often co-occurs, as described previously. Hence, AD, DLB, PDD and PD may be different points on a continuum [73,79,136], in which composition of pathological burden and differences in regional distribution are related to clinical features (see figure 2). At one pole: PD, with Lewy body pathology and cell loss in brainstem nuclei; while in PDD and DLB, additional widespread cortical Lewy bodies, Aß plaques and mild hippocampal atrophy. At the other pole: AD, characterized by Aß depositions, tau pathology and progressive cortical atrophy. DLB patients with tau pathology are often considered mixed AD and DLB [136]. In a study by Kraybill et al., patients with double pathology at autopsy (AD and DLB) had exhibited more rapid cognitive decline compared to those with AD or DLB pathology alone [139]. Another autopsy study by Jellinger et al. reported shorter survival length in DLB patients with concomitant AD pathology [140].
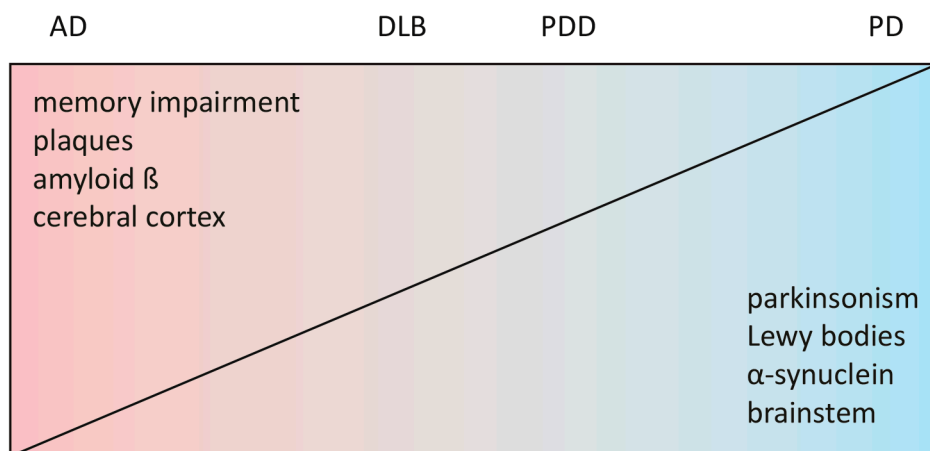
FIGURE 2: The AD-DLB/PDD-PD continuum.
Memory imparment and Parkinsonism are the cardinal symptom of AD and PD respectively. Plaques and amyloid ß are the neuropathological hallmarks of AD. Lewy bodies and α-synuclein are essential findings in PD pathology. In AD, there is a progressive atrophy of cerebral cortex, while in PD neurodegeneration is typically most pronounced in brainstem nuclei. In DLB and PDD, AD and PD characteristics overlap and individuals may have different proportions of the two pathologies

Furthermore, cerebrovascular disease may impact the clinical presentation. Cerebrovascular pathology occurs to some extent in almost all AD cases [141], but its contribution to cognitive impairment and the clinical progression is questioned. In one study of severe AD, minor vascular changes were found not to influence cognitive decline [142]. Others suggest that cerebrovascular disease may have an additive effect on AD pathology, resulting in earlier and more severe dementia [143,144,145,146]. The term mixed dementia is used to describe cases fulfilling both criteria for vascular dementia (VaD) and AD [147]. Cerebrovascular lesions (CVLs) are also common in PD and PDD, but for some reason less frequent in DLB [148]. Such vascular lesions are known to influence the development of parkinsonism [149] but their impact on cognition in PD, PDD and DLB remains unclear [148].

In respect of this complexity, a recent review stressed the importance of assessing more than one pathological feature when diagnosing dementia syndromes [136], also recommended by the DLB Consortium [53]. Diagnostic accuracy, well-designed sampling methods, and carefully prepared grouping procedures, are important to enable comparisons necessary in the search for reliable prognostic markers.

2.3. Potential prognostic markers

2.3.1. Biochemical markers

Cerebrospinal fluid (CSF) is the liquid surrounding the central nervous system. Biochemical changes in the brain are often readable in protein densities in the CSF, and many investigators have set out to examine biomarkers in CSF hoping these would mirror the underlying neuropathological process in AD and other types of dementia. *Aß42, total tau (T-tau) and phosphorylated tau (P-tau) in CSF* have emerged as leading diagnostic and potentially prognostic fluid biomarkers in AD [150] and e.g. in Sweden they are incorporated into routine clinical assessment. They are used mainly for diagnostic purposes, as a low Aß42 level along with elevated T-tau and P-tau levels, is a sensitive and specific indicator for AD [151], also in clinical settings [152]. The pattern described above also predicts conversion of MCI to AD with high sensitivity and specificity [153]. Furthermore, *T-tau alone* has a potential role as a prognostic marker in AD. High CSF concentration of T-tau is found in several disorders that present with neuronal damage, e.g. transiently after brain trauma [154] and after ischemic stroke [155]. In the latter, levels correlates with the size of infarction [156]. In Creutzfeldt-Jacobs disease (CJD), which bears extensive neurodegeneration, T-tau levels are extremely high [157,158]. In AD patients, levels of T-tau are moderately elevated [151] and stable over time [159,160]. Based on this, one might suggest that T-tau reflects the current intensity of axonal degeneration at any given time, rather than the accumulated neuronal loss [161,162]. High T-tau has previously been reported to predict a poorer prognosis in AD [163] and in DLB [164]. Another potential biomarker in DLB is *CSF α-synuclein*. A recent meta-analytic study concluded that α-synuclein may have diagnostic utility discriminating DLB from AD [165], as levels in CSF are found to be lower in DLB compared to AD [165,166].

Substantial effort has been put on transferring the CSF tests to reliable blood tests. For the analysis of tau, the biochemical methods are not yet successful and for Aß, levels in CSF and plasma have been found not to correlate [162]. Concerning other markers in plasma, one study reported data suggesting that high levels of *homocystein* are predictive for a more rapid cognitive decline in AD, and may reflect regional cerebral hypoperfusion [167].

2.3.2. Clinical markers

Demographical characteristics

Age at onset has been studied for prognostic value, but results are conflicting. According to some studies, earlier age at onset is associated with more rapid pro-

gression in AD [168,169,170,171,172] and one study shows this in DLB [169]. However, others show that later (older) age at onset is associated with a more aggressive disease course [140,173,174]. Indeed, some studies obtained no correlation between age at onset and prognosis [175,176]. *Higher level of education* has been associated to more rapid cognitive decline [129,172,177,178], but in other studies level of education had no impact on prognosis [175,179]. It has been suggested that higher level of education adds to the cognitive reserve that may mask early symptoms, and once dementia is manifest, the patient is already at a more severe stage of the disease [131,180]. This would explain the poorer prognosis for those with higher education, as reported in some studies.

Cognition

Cognitive status at baseline could provide prognostic information. Linguistic deficits [173,178,181,182,183,184] as well as attentional and executive dysfunction [185] have been reported to predict rapid illness progression in AD. A higher *degree of severity at baseline* (measured by MMSE) correlates with a more rapid rate of progression [186]. Furthermore, the *rate of cognitive decline in earlier stages* may predict rapid decline during later stages of AD as well [186,187,188].

Type of dementia

Several studies sought to identify differences in progression rate or survival time between AD and DLB. The majority report a shorter survival time in DLB [49,189,190,191,192,193,194,195,196], but some did not find any differences in survival time [197,198,199,200] between AD and DLB (Table 3). The rate of cognitive decline is most often reported to be equal between the two diagnostic groups [201,202], but studies have also reported faster [192] and slower [203] progression in DLB. This inconsistency may be partly explained by methodological shortcomings, e.g. retrospective study design, differences in the selection of study subjects and the absence of a clear starting point in many longitudinal studies comparing survival (Table 3). Most studies measure survival time from "disease onset", which is an imprecise starting point compared to, for example, "time of earliest symptoms".

Associated clinical symptoms

Associated clinical symptoms have often been reported to influence length-of-survival or rate of cognitive or functional decline. *Poor nutritional status* [204], have been reported to impact prognosis negatively. Presence of *hallucinations* predicts a more rapid progression in AD [205,206,207], as well as in both DLB [208] and PDD [209]. *Extrapyramidal symptoms* (EPS) are associated with poorer prognosis in AD patients [210,211,212,213,214], even though the definition of EPS differed between studies. Since both hallucinations and EPS are characteristic features of

DLB, this agrees with autopsy studies showing that double pathology implies a poorer prognosis [139,140]. Concomitant *vascular pathology, cardiac disease and vascular risk factors* may not only increase the risk of developing dementia, but also influence prognosis negatively. Ischemic and congestive heart disease, diabetes and hypertension have all been associated with more rapid cognitive decline [215] and shorter survival [189,214], even though some studies report no effect on prognosis [171,215,216,217]. The prognostic impact of vascular morbidity may be equal for persons with and without dementia [218,219]. A recent review proposes *cardiovascular autonomic failure* as a potential prognostic marker in Lewy body disorders [220].

2.3.3. Brain imaging markers

Neuroimaging supplements clinical examination in order to exclude other causes for dementia, i.e. cerebral hemorrhage, intra cerebral tumor, normal pressure hydrocephalus or significant vascular lesions. It is also used to discriminate types of dementia [see review, 23]. Increasingly, studies indicate that imaging methods may be surrogate markers for disease progression and therefore valuable tools to detect effects from disease modifying drugs [221]. For example, Jack et al. [222] followed 64 AD patients to investigate annualized *change in MRI atrophy measures*. Cognitive performance scores were used to group patients into slow- versus fast-progressor groups. The authors found that rate of change in MRI atrophy measures is positively correlated with rate of disease progression. Moreover, Wahlund et al. reported that CSF T-tau level correlates with rate of hippocampal atrophy in AD patients [223]. The potential prognostic value of knowing the *pattern of brain atrophy* is highlighted in Sluimer et al. [224] who in an MRI study identified in a group of AD patients more generalized than localized (hippocampal) brain atrophy. Generalized atrophy, together with young age at onset and absent APOE4, were found to associate with faster loss of brain volume.

New imaging techniques hold promise for understanding prognosis. During the last decade, advanced methods to visualize molecular compounds of neurodegenerative dementia have been developed. Information on glucose metabolism (FDG-PET) and Aß load (PIB-PET) may be obtained using PET [150]. Interestingly, PET tracers for tau pathology [225] and inflammation [150] are being developed, which add to the available biological markers to study prognosis and to monitor response to disease modifying therapies.

Table 3. Studies comparing length of survival in AD and DLB

Author	n=	Length of survival as main outcome	Reported study design	Starting point	Measure	Difference in survival
Magierski et al. 2010 [189]	51 DLB 183 AD	Yes	Retrospective	Time of dementia diagnosis	Mean time to death	DLB shorter
Hanyu et al. 2009 [190]	56 DLB 111 AD	Yes	Prospective	First visit	Survival analysis, 5 yrs log rank test (time to endpoints: admission, death or institutionalization)	DLB shorter
Williams et al. 2006 [191]	63 DLB 252 AD Autopsy confirmed	Yes	Prospective	Disease onset	Survival analysis, 25 yrs log rank test (time to death)	DLB shorter
Walker et al. 2000 [197]	32 DLB 43 AD	Yes	Retrospective	Disease onset First presentation at psychiatric services	Survival analysis, 3 yrs log rank test (time to death) and Mean time to death	No difference No difference
Heyman et al. 1999 [198]	27 DLB 74 AD Autopsy cases	Yes	Prospective[a]	Study baseline	Mean time to death	No difference
Olichney et al. 1998 [192]	40 DLB 148 AD Autopsy cases	Yes	Retrospective[b]	Disease onset Study baseline	Mean time to death	DLB shorter No difference
Weiner et al. 1996 [200]	24 DLB 58 AD Autopsy cases	No	Retrospective	Disease onset First evaluation	Mean time to death	No difference No difference

Study	Cases					
Klatka et al. 1996 [199]	28 DLB 58 AD Autopsy cases	No	Retrospective	Disease onset	Mean duration of illness	No difference
Lippa et al. 1994 [193]	5 DLB 7 DLB+AD 5 AD Autopsy cases	No	Retrospective	Disease onset	Mean duration of dementia	DLB shorter? [c]
McKeith et al. 1994 [194]	20 DLB 21 AD Autopsy cases	No	Retrospective	First presentation at specialist unit	Mean time to death	DLB shorter
McKeith et al. 1992 [195]	21 DLB 37 AD Autopsy cases	No	Retrospective	First onset of symptoms	Mean time to death	DLB shorter
Hansen et al. 1990 [49]	13 DLB 23 AD Autopsy cases	No	Retrospective[d]	Time of earliest symptoms First examination	Mean time to death	DLB shorter No difference
Perry et al. 1990 [196]	18 DLB 46 AD Autopsy cases	No	Retrospective	Disease onset	Mean time to death	DLB shorter

[a] The autopsy cases in this study were all drawn from a registry for AD (CERAD) and all had a premortem diagnosis of AD. Clinical data of all patients in this study seems to be prospectively collected. [b] The subjects were selected from 3 different neuropathology series and clinical data seems to be retrospectively collected in two of them. [c] Average survival time is shorter in DLB and DLB+AD (5 yrs and 6 yrs resp) compared to AD (6,8 yrs), but no statistical comparison is performed. [d] Some subjects had been evaluated during life as a part of longitudinal follow-up studies, and some had been evaluated clinically in a geriatric outpatient clinic

2.3.4. Genetic markers

Variations in APOE4 [226,227,228,229,230] and interleukin -1 alpha [231] geno-
types have been reported to affect the rate of progress in AD. The effect of APOE on
disease progression seems to be dependent on disease stage [131], which possibly ex-
plains to why other investigations have failed to find any association between APOE
genotype and prognosis [178,232,233]. Genetic variation in buturylcholinesterase
(BuChE) has also been associated with the rate of cognitive decline in AD [234].
Interestingly, Perry et al. found that DLB patients with lower levels of BuChE activ-
ity in cortex have slower cognitive decline [235]. Farrer et al. used an algorithmic
model that identified a major genetic locus for AD, including several genetic factors,
which predicted the clinical course, at least in men but not women with AD [236].

In summary

Despite considerable effort to identify prognostic markers in neurodegenerative de-
mentia, biomarkers are not available that reliably predict time to death or rate of
cognitive decline. This may reflect methodological shortcomings in earlier studies,
but also the complex nature of neurodegenerative dementia disorders.

3. Aims

3.1. General aim

The general aim of this thesis is to identify, review and qualify possible indicators, including biological markers to predict course and time of survival in the two most common types of neurodegenerative dementia; AD and DLB/PDD.

3.2. Specific aims

To test the hypothesis that CSF total-Tau is associated with the degree and profile of cognitive impairment, as well as the rate of cognitive decline during follow-up in AD patients.

To study differences in survival between AD patients and patients with DLB. Since anamnestic and retrospective information about disease duration are unreliable variables, we measure survival from a fixed cognitive level.

To investigate the frequency of symptoms related to autonomic dysfunction (orthostatic hypotension, constipation and urinary incontinence) in a DLB/PDD population and to find out whether its presence or severity is correlated to a shorter survival in these patients.

To investigate the influence on survival time of treatment using memantine in patients with DLB and PDD and to study the potential prognostic value of a positive response to treatment.

4. Methods

4.1 Studies

All patients in the following studies were recruited during routine clinical visits, with the exception of the Memantine Study (see below). Procedures for each patient included: clinical interview as well as physical, neurological and psychiatric examinations prior to inclusion; cognitive testing and computed tomography (CT) of the brain. All studies were approved by the Ethics Committee at Lund University.

4.1.1. Malmö Alzheimer Study (MAS)

Patients included in the Malmö Alzheimer Study (MAS) were investigated at the Memory Clinic at Skane University Hospital in Malmö between 1999 and 2003. The study design was cross-sectional as all data were collected at baseline. To be included, each patient had to *i)* meet both DSM IV criteria [2] for dementia, and NINCDS-ADRDA criteria [6] for a diagnosis of probable AD *ii)* complete baseline assessment, including routine blood samples, blood pressure measurement, cognitive testing, CT or MRI of the brain, investigation of regional cerebral blood flow and lumbar puncture; and *iii)* be living at home (mild-to-moderate dementia). The exclusionary criterion was advanced vascular pathology on CT.

    The original study population consisted of 274 patients. However, after later reviewing the diagnosis, only 264 remained. Of the 264 patients in MAS, 142 were also followed longitudinally in SATS (see below).

4.1.2. The Swedish Alzheimer Treatment Study (SATS)

The Swedish Alzheimer Treatment Study (SATS) was conceived to investigate long term effects of ChEI treatment on AD patients in a routine clinical setting. It is a is a prospective, open label, three-year follow-up study and inclusionary criteria included: *i)* > 40 years old, *ii)* NINCDS-ADRDA diagnosis of probable AD [6], *iii)* living at home, *vi)* having a responsible caregiver, and, *v)* being assessable with

MMSE [237]. Exclusionary criteria included *i)* ongoing treatment with ChEI or *ii)* meeting criteria for contraindications to ChEI therapy. Treatment with ChEI was initiated at baseline. In 1997, only donepezil was on the market but when rivastigmine and galantamine became available, the choice as to which ChEI to use and at what dosage was left as to physician judgment.

The SATS patients were assessed during a 3-year, structured follow up program that included assessments (cognitive testing, ratings of ADL and global testing) at baseline, after 8 weeks, after 6 months and thereafter semi-annually until 36 months.

Patients (in total, n= 1,258) were recruited from 14 memory clinics in Sweden, and they began treatment with ChEI between 1997 and 2008. In this thesis, only patients from the memory clinic in Malmö (n=425) were included. For further information about SATS, please see the detailed description in Wallin et al [238].

4.1.3. DLB follow-up study

A follow-up study of Dementia with Lewy bodies was designed that included patients referred to the memory clinic at Malmö University Hospital Malmö between 1997 and 2004. Fifty-six patients were included, but after longitudinal follow-up, during which the diagnosis was reviewed by more than one physician, only 49 patients remained. These were evaluated to fulfil the clinical diagnostic criteria of probable DLB according to the 1995 consensus [50]. Seven patients were examined postmortem and DLB was confirmed in each case.

4.1.4. The Memantine Study (MEMDLBPDD)

A randomized and double-blinded, placebo-controlled trial (RCT) of memantine was conducted in 2005–2008 [84], in which 75 patients with mild-to-moderate DLB or PDD (MMSE ≥ 12), recruited from psychiatric, memory and neurological outpatient clinics in Norway, UK and Sweden were included. Patients were assigned to placebo or memantine treatment (20 mg daily) and assessed at baseline, 12 and 24 weeks. All patients met the revised consensus criteria for DLB [53] or fulfilled the clinical diagnostic criteria according to the UK Parkinson's disease Society Brain bank and subsequently developed dementia (by DSM IV criteria) [2] more than a year from onset of motor symptoms (PDD).

The Swedish population consisted of 42 patients. After the original RCT, they continued with a 4-week washout period followed by open-label treatment and ordinary yearly clinical visits within a structured follow-up program at our clinic. Patients remained double-blinded during wash out, but not during the open label treatment. The (double blinded) medication administration was discontinued at the end of the RCT without sequentially decreasing the doses. The open-label medi-

cation doses were increased during a titration period of 4 weeks until the dosage reached 20 mg daily. Each individual's informed consent to participate in the study was renewed before that individual entered the open-label treatment follow up.

4.2. Study populations

Table 4. Populations in Papers I-IV

Paper	Diagnosis	Number of patients	Sample from study
I	AD	142	MAS, SATS
II	AD	79	MAS, SATS
	DLB	49	DLB follow-up
III	DLB/PDD	30	MEMDLBPDD
IV	DLB/PDD	32	MEMDLBPDD

4.2.1. Paper I

One hundred and forty-two patients with AD included in the Malmö Alzheimer Study (MAS) were selected to participate in this study. These 142 AD patients had also been followed longitudinally while being treated with ChEI in the Swedish Alzheimer Treatment Study (SATS) during a 3-year period.

4.2.2. Paper II

The 79 AD patients in Paper II were selected from MAS, and they were included in SATS during the period of 1997–2003. Later, in 2007, they also underwent a reevaluation of the diagnosis based on medical reports where they were assessed as having probable AD. The 49 DLB patients in Paper II, were selected from the DLB follow-up study.

4.2.3. Paper III

The study population in Paper III constitutes the 30 patients (16 DLB, 14 PDD) from the Swedish population (total n = 42) in the MEMDLBPDD study, who underwent assessments including orthostatic blood pressure testing at all three visits during the follow-up (at baseline, week 12 and week 24).

4.2.4. Paper IV

The study population in Paper IV constitutes the 32 patients (16 DLB, 16 PDD) from the Swedish population (total n = 42) in the MEMDLBPDD study, who completed the 24 week follow-up.

4.3. Measures

Table 5. Measures and main statistics in Papers I-IV

Paper	Grouping variable	Main Statistics	Primary outcome measure
I	CSF -T-tau -P-tau -Aß42	Person's Chi-squared test (χ²) Student' *t*-test Mann Whitney *U* test Spearman correlation	Change in -MMSE -ADAS-cog over time
II	Type of dementia	Person's Chi-squared test (χ²) Student' *t*-test Mann Whitney *U* test Log-rank test Multivariate Cox Regression analyses	Survival from - time of onset - time of diagnosis - MMSE 17±1 - MMSE 20±1
III	Orthostatic blood pressure measurements History of - urinary incontinence - constipation	Person's Chi-squared test (χ²) Mann Whitney *U* test Log-rank test	Survival from baseline
IV	-Treatment yes/no -Treatment response (CGIC)	Person's Chi-squared test (χ²) Mann Whitney *U* test Log-rank test	Survival from baseline

4.3.1. Cognitive tests

Cognitive testing was administered at the Memory Clinic at Skane University Hospital in Malmö, Sweden, by several experienced nurses.

MMSE (Paper I-IV)

The Mini-Mental State Examination (MMSE) [237] was used in all studies. It is widely used in clinical practice as a cognitive screening instrument. Its scores range from 0-30, a higher score indicating a better cognitive performance. It is easy to administer and takes about 10 minutes to complete. It samples performance in domains, including memory, attention, orientation, language and visuo-construction. The MMSE has been shown to be sensitive to identify moderate to severe cognitive impairment. A score of <24 is generally accepted as indicating cognitive impairment,

consistent with recommendations in the literature [239]. Many investigative clinical trials in drug development of AD restrict the MMSE range to 10-25 at baseline [129]. Although, devised as a screening tool, MMSE is often used to track changes in cognition over time, in clinical practice as well as in research. However, such use has been criticized since it is a weak instrument to measure change in early stage dementia [240], and in later, severe stages [239]. Floor and ceiling effects must be taken into consideration when measuring performance using the MMSE. Whether these effects are due to a true variation in the rate of cognitive decline during the clinical course or to poor sensitivity of MMSE is questioned [129]. In AD, the mean annual decline has been reported as 2 to 4 points per year in cohort studies [129]. There is no consensus on what should be considered a clinically relevant change in MMSE, but 3-5 points is suggested in different studies [241,242,243,244]. To some extent, it seems like MMSE can be used to demonstrate the cognitive profile characterizing specific dementia disorders. In a sample of 33 patients with MMSE score 21-27, Palmquist et al. [245] identified that the criteria MMSE orientation score x3 ≥the total MMSE score, could separate DLB patients from AD patients with a sensitivity of 100% and a specificity of 57%.

ADAS-Cog (Paper I)

Alzheimer's Disease Assessment Scale (ADAS-Cog) [246,247] was designed to measure treatment efficacy in patients with AD, and today it is the most widely used test in clinical trials on patients with AD [248]. It takes 20-50 minutes to administer and can yield scores ranging from 0-70, a higher score indicating more severe impairment. Eleven domains of cognitive ability are tapped by ADAS-Cog, including memory, orientation, language construction and praxis, which mean that domains typically affected in AD are well covered. Comparatively, the ADAS-Cog is a more powerful measure of cognitive impairment in AD than a screening tool like the MMSE. The ADAS-Cog does not measure attentional deficits, executive dysfunction and agnosia. Consequently, its use might be avoided in types of dementia where such disabilities are typically present. Measured with ADAS-Cog, the rate of deterioration is high in moderate stages of AD, compared to mild or very severe stages [248,249]. As discussed with regard to the MMSE, such testing result could either be due to the mode of progression of the disease itself or a limitation of the test [248]. The mean annual change in ADAS-Cog score in mild to moderate stages of AD is reported to be 5.5 [250], but in moderate stages, reported as high as 9-12 points [249].

4.3.2. Investigation of motor impairment

UPDRS (Paper IV)

The Unified Parkinson's Disease Rating Scale (UPDRS) [251] was developed to monitor PD-related disability and impairment. The scale itself consists of four units: Part 1) Mentation, behavior and mood, Part 2) Activities of daily living, Part 3) Motor, Part 4) Complications. One of the core advantages of UPDRS is that it captures multiple aspects of PD. It is considered efficient, fairly comprehensive and is applicable across the clinical spectrum of parkinsonism. Of available scales, UPDRS is currently the most widely used to assess parkinsonian motor impairment and disability [252]. In Paper IV, motor impairment is evaluated with UPDRS and included as baseline characteristics.

4.3.3. Neurochemical methods

CSF (Paper I, II)

Lumbar puncture was performed in the sitting position and CSF samples were taken at the L3/L4 or L4/L5 interspaces. The first portion of CSF (1 mL) was discarded and the following 10mL was collected and centrifuged at 2000g at 48C for 10 min to eliminate cells and other insoluble materials. The CSF samples were immediately frozen and stored at -80C. CSF T-tau, P-tau and Aß42 levels were analyzed as previously described [153].

4.3.4. Investigation of autonomic dysfunction

Orthostatic hypotension (Paper II-IV)

Blood pressure measurements and performance of orthostatic tests are central in Paper III but were included as baseline characteristics in Papers II and IV as well. These were obtained using a validated digital spyngomanometer (OMRON M5-1) over the brachial artery [253]. The performance of an orthostatic test followed a standardized scheme where blood pressure and pulse rate were recorded after at least ten minutes rest in supine position, immediately after standing up, and repeated after one, three, five and ten minutes of standing. All patients stood up without assistance. Orthostatic hypotension is defined as a reduction in systolic blood pressure of at least 20 mmHg or a reduction of diastolic blood pressure of at least 10 mmHg, as recommended by The Consensus Committee of the American Autonomic society and the American Academy of Neurology [254]. In Paper III, we wanted to determine the grade of orthostatic hypotension. Each patient performed three orthostatic tests during the follow up (at baseline, after 12 weeks and 24 weeks). We analyzed

each patient´s diastolic and systolic values individually and each measurement point was dichotomized as orthostatic or not orthostatic. The sum of all orthostatic values (5 measure points at 3 assessments, systolic and diastolic, i.e. max 30 values) in each patient was calculated.

Other symptoms of autonomic dysfunction (Paper III)

Together with orthostatic hypotension, urinary incontinence and constipation are the most common features of autonomic dysfunction. In order to identify urinary incontinence we used the Disability Assessment for Dementia (DAD) [255]. This scale evaluates the basic and instrumental activities in daily living of people with dementia. It consists of 40 items, addressing the following functional domains: hygiene, dressing, continence, eating, meal preparation, telephoning, going on and outing, finance and correspondence, medication, leisure and housework. It takes about 15-20 minutes to administer. To evaluate continence, the following questions are asked to the patient and the caregiver 1) "During the past two weeks, did (name) decide to use the toilet at appropriate times, without help or reminder?" 2)"During the past two weeks, did (name) use the toilet without 'accidents', without help or reminder?" In our study, urinary incontinence was defined as a negative answer to any of these two questions. Constipation was defined by regular use of purgatives and/or enemas.

4.3.5. Assessment of treatment effect

Clinical Global Impression of Change (Paper IV)

Treatment response in Paper IV was measured by The Clinical Global Impression of Change (CGIC) [256]. The CGIC assigns values based on a clinical interview data from the patient and her caregiver. The interviews are lengthy and detailed and must be administered by experienced clinicians. The doctor's overall impression is translated into rating on a categorical scale ranging from 1-7, with a low score indicating clinical improvement. A baseline score is obtained as a measure of the global condition, and during follow up the CGIC assesses the change compared to baseline. Studies report fair to moderate test-retest reliability of the global scales, and fair to very good inter-rater reliability. Fair to very good construct validity has been reported [257]. Thus, the validity and reliability of global scales, as well as sensitivity to detect change is unclear and needs further elucidation.

4.3.6. Survival as primary outcome measure (Paper II-IV)

Death is the natural and final endpoint of the clinical course of dementia and we know that dementia shortens life [218,258,259,260]. There have been conflicting estimates of the time of survival following a diagnosis of dementia, but most studies report survival-years-post-diagnosis between 5-10 years [260]. Compared to other clinical milestones, e.g. nursing home placement or cognitive or functional deficits, death is a distinct and more culturally independent clinical event. The time of death can be recorded in all patients. Hence, the choice of survival as the outcome measure and survival analysis as the statistical approach, eliminates the potential bias effect from selective loss of patients [187] and the statistical limitations following a high drop-out rate in already small study samples. However, a number of studies highlight the risk that patients with a rapidly progressive disease course are excluded from or to a lesser extent included in follow-up studies, leading to underestimation of survival time [258,261]. This is referred to as survivor or length bias and its risk is higher in studies measuring survival from study entry rather than from time of onset [258]. In general, reviews on mortality in dementia have had to contend with inconsistent terminology including terms, such as, disease duration, years with disease, survival from first time of evaluation and onset of dementia [259]. Age seems to have major influence on survival in dementia [218]. For example, Brookmeyer et al. found that the younger one's age at AD diagnosis, the longer the survival: at age 65, median survival was 8.3 years, while at age of 90 years it decreased to a median 3.4 years survival [261]. Male gender, disease severity, type of dementia, diabetes, cardiovascular disease and cancer are in most studies associated with higher mortality [218,260]. Therefore, these factors, and age, should be taken into consideration [260] and adjusted for in survival analyses. Ideally, the cause of death should also be taken into consideration, since it is important to know how many die because of dementia per se [259], though these cases may be hard to discriminate. The major causes of death in dementia are cachexia/dehydration, pneumonia (from associated somatic decline or swallowing problems) and cardiovascular disorder [262,263].

Survival is the primary outcome measure in Papers II-IV. In Paper II, we investigated differences in survival time between AD patients and DLB patients. In each groups, survival was measured from several selected clinical starting points, including: time of reported disease onset, time of diagnosis, time of MMSE score 20±1 and time of MMSE score 17±1. In Papers III and IV survival was measured from study baseline, which coincides with the time when all patients started treatment with memantine or placebo.

4.4. Statistical methods

In all papers, statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software (version 16.0, 17.0, 18.0 and 21.0 for Windows, SPSS, Inc., Chicago, IL, USA). Med Calc (version 12) was used for Receiver Operator Curve (ROC) analysis in Paper III.

Cathegorical demographic variables were analyzed using Pearson's chi-square test. For variables with normally distributed data, Student's *t*-test was used to compare the differences between the means in two independent groups. In Paper I, age and follow-up time were considered normally distributed. In Paper II, the Kolmogorov-Smirnov statistic was used to analyze that age was normally distributed. When data was not normally distributed and/or when the sample size was too small, median values were used and Mann-Whitney U test was performed to compare continuous variables between two independent groups. Spearman rank correlation coefficient (r_s) was used to analyze the linear relationship between non-normally distributed, continuous variables (CSF biomarker levels and Cognitive test scores in Paper I). Kaplan Meyer curves were performed to illustrate the survival distribution in two groups and the Log-rank test was computed to compare survival between groups (Papers II-IV). Multivariate Cox Regression models (enter method) were performed in Paper II to investigate the effects of possible covariates on survival. Level of significance was defined as $p<0.05$ in all papers.

5. Summary of Results

5.1. Paper I

The first study was informed by earlier studies reporting transient elevation of T-tau in brain trauma [154], viral encephalitis and clinically active multiple sclerosis [264]. T-tau levels are elevated after a cerebral stroke [155], and such levels correlate with lesion size [156]. Moreover, the highest T-tau levels are seen in disorders with the most intense neuronal degeneration, e.g. Creutzfeldt-Jacobs disease [157,158]. In an MRI study of an AD sample, Wahlund and Blennow reported a positive correlation between CSF T-tau level and annual change in ventricular volume, i.e. decreasing brain tissue mass [223].

The hypothesis in Paper I was that higher T-tau level in CSF is associated with more rapid clinical deterioration. We repeatedly examined cognitive performance during a three-year period, including test scores from the MMSE and ADAS cog. We also hypothesized that CSF T-tau levels correlate with the degree and profile of cognitive impairment.

We noticed in a histogram showing T-tau concentration levels in CSF obtained from 142 AD patients that these were bimodally distributed, intersecting at about 800 ng/L. After statistical investigation we also found that 800 ng/L corresponded to the upper quartile. In this sample 34 (24%) of the patients had T-tau levels above 800, which we considered as very high. Corresponding groups were constructed based on P-tau and Aß42 levels, where cut off values (110 ng/L and 400 ng/L respectively) represent the upper quartile.

We investigated the correlation between biomarker concentration in CSF and cognitive performance on the MMSE and ADAS cog at baseline. Also, in the course of follow-up, we examined the rate of cognitive performance decline. Biomarker concentration in CSF was computed alternately, as continuous data as well as in dichotomous groups.

Results

Baseline scores and rate of cognitive decline

- Higher T-tau and P-tau concentrations correlated with lower MMSE total score (r_s=-0.27, p=0.001; r_s=-0.25, p=0.003) and with higher ADAS Cog score at baseline (r_s=0.24, p=0.001; r_s=0.18, p=0.03). No correlation was obtained between Aß42 concentration level and cognitive performance scores at baseline.

- The patient group with T-tau >800 ng/L performed significantly worse than the group with T-tau ≤800 ng/L based on MMSE (p=0.002) and ADAS-cog scores (p=0.003). Also, P-tau >110 ng/L was associated with lower scores MMSE at baseline (p=0.02). However, performance on ADAS-Cog did not discriminate between the two P-tau groups. When patients were divided into two groups based on Aß42 levels, scores at baseline did not discriminate.

- Patients with higher levels of T-tau showed more rapid performance decline on the MMSE (points/months) during the follow up, when computed as continuous data (r_s=-0.23, p=0.008), and by comparison in dichotomous groups (p=0.013) (Figure 3a). However, T-tau levels had no significant effect on rate of deterioration in ADAS-Cog scores (points/months) (Figure 3b).
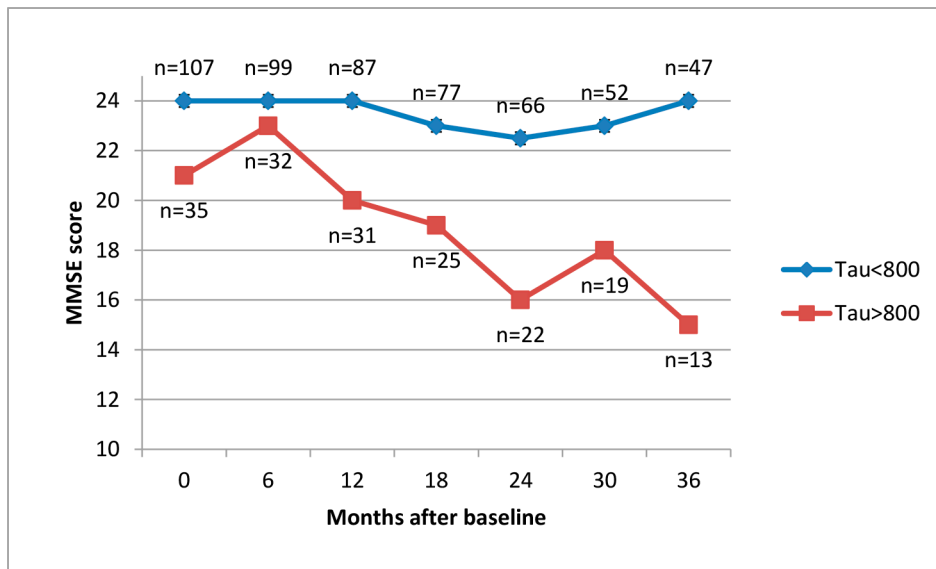
Figure 3a. MMSE scores in the two T-tau groups, during the 3-years follow-up. Every point represents the median score at baseline and at the six following visits. N=number of patients.
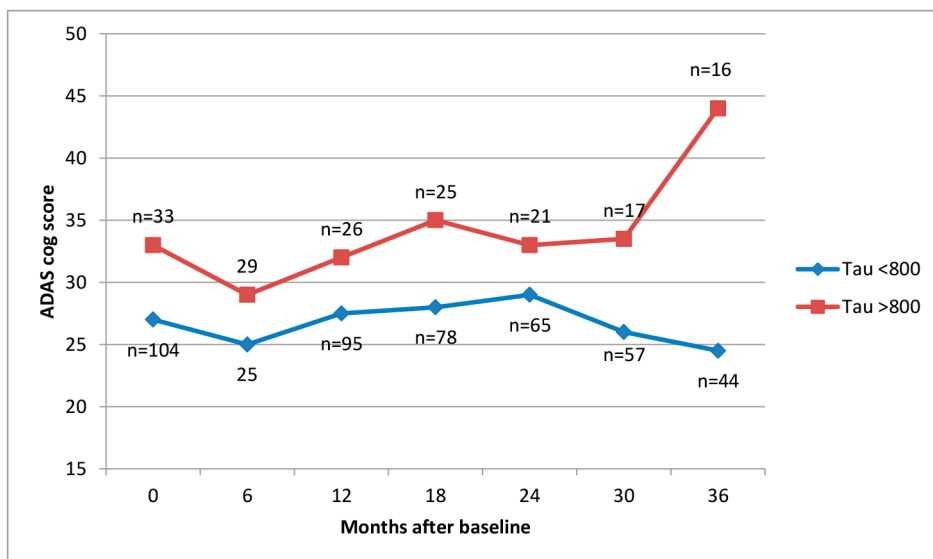
Figure 3b. ADAS-Cog scores in the two T-tau groups, during the 3-years follow-up. Every point represents the median score at baseline and at the six following visits. N=number of patients.

- No correlation was obtained between either P-tau levels or Aß42 levels and rate of performance decline on either MMSE or ADAS-Cog scores.

Cognitive profile

- Patients with T-tau >800 performed worse on the MMSE-Orientation (p=0.003) and –Copying tasks (p=0.02), and on the ADAS-Cog-Orientation (p=0.001) and -Delayed recall memory (p=0.004).

- Patients with P-tau >110 n/L performed worse on the ADAS-Cog-Orientation (p=0.03) and the MMSE-Verbal ability (p=0.02).

- In the two groups based on Aß42 concentration, there were no significant differences in performance on the subunits of MMSE or ADAS-Cog.

Comments

In this study (Paper I) we investigated the potential role of CSF biomarkers and T-tau levels in particular, as prognostic markers during the clinical course of Alzheimer's disease. We found that very high levels of CSF T-tau were associated with lower performance on cognitive tests at baseline, regardless whether continuous or dichotomous data was were used for comparison. Patients with very high levels of T-tau exhibited more rapid decline in performance on the MMSE during

the 3-year follow-up. However, this finding may be undermined since no significant differences were observed when ADAS-Cog scores were used, and ADAS-Cog has been considered the more sensitive of the two measures. We also found that very high T-tau levels were associated with a deviating cognitive profile, when assessed with MMSE and ADAS-Cog. We reasoned that patients with very high levels of T-tau may represent a subgroup of AD patients who present with more pronounced deficits in orientation and memory.

Our results are in line with two more recent publications [265,266] on the role of T-tau in AD. These two studies have a more thorough statistical performance. Multivariate linear mixed models were used to study the association between CSF biomarkers and rate of cognitive decline [266], and cluster analysis was used to identify subgroups defined by the three CSF biomarkers; T-tau, P-tau and Aß42 [265]. The use of MMSE was limited to describe only disease severity while a more comprehensive and rigorous neuropsychological test battery was used to evaluate separate cognitive functions, and this may be more appropriate since the different tasks in MMSE have shown only modest correlation to corresponding neuropsychological tests [267,268].

In our study, the low-tau (<800) patient group were found to remain stable in MMSE scores for 3 years. This was not expected in an AD cohort, but this finding may indicate a ceiling effect on performance scores in patients with early stage AD and only mild cognitive deficits that the MMSE does not detect.

The study population consisted of 142 patients with AD. All began treatment with ChEI at baseline and were prospectively followed during 3 years in a structured program. After 3 years only 60 (58%) patients remained. No significant differences were obtained for age or duration of disease between patients who finished the follow-up and drop-outs, but the drop-outs performed worse on both MMSE and ADAS-Cog at baseline. Presence of concomitant hypertension or diabetes did not dissociate the groups either. A strategy used to compensate for the great proportion of drop-outs was to calculate change in cognitive test scores per month.

If the hypothesis that T-tau levels reflect the rate of neuronal degeneration is true, then levels of T-tau would decrease as a response to a disease-modifying drug. To our knowledge, only one study has reported a decrease in T-tau and P-tau levels following Aß passive immunization in AD patients [269]. Biomarkers to monitor effects of potentially disease-modifying treatments are lacking and would be of great value. The idea of identifying subgroups of AD patients, such as on the basis of characteristic CSF profiles, has been more current recently, since the heterogeneous nature of AD has drawn more attention [132,133]. Likely, future therapies will be individualized to suit clinical subgroups rather than all patients with a diagnosis of AD.

After the publication of this study, we returned to investigate the relationship between T-tau levels and atrophy measures on computed tomography in the same population. High- T-tau (>800 ng/L) patients were found to have more pronounced atrophy in temporal regions, as compared to patients with low-T-tau (<800 ng/L).

Patients with very high T-tau levels could be expected to exhibit the most distinct AD symptoms and the most pure AD pathology.

5.2. Paper II

In Paper II, we compared the lengths of survival between patients with AD and patients with DLB. We hypothesized based on clinical experience that prognosis is poorer in DLB compared to AD.

Information on how life expectancy compares across different types of dementia as well as between subgroups of patients within the diagnostic groups is important to understand and describe these diseases.

One of the obstacles to compare results across earlier studies is that the chosen starting point varies between studies and, thus, average-survival time is measured differently, i.e. when calculated from onset of symptoms, from time of diagnosis or from study entry.

In our study, we wanted to match patients on one stage, to enable a more meaningful comparison of length-of-survival between AD and DLB samples. Staging is a well-established strategy when estimating time to endpoints in other areas of clinical practice, e.g. when marking labor and delivery time-points or in the care of cancer patients. Staging is important in the planning of treatment and when explaining to patients and families what to expect as the disease progresses. As discussed by Kraemer et al., staging may be methodologically important, especially when the timing and clinical course is heterogeneous among patients [270].

The study sample consists of 128 patients attending our memory clinic, 79 with AD and 49 with DLB. All patients participated in a structured follow-up program, the intention of which was to administer the MMSE to patients every 6 months through a 3-year period. This allowed us to compute time-to-death from selected time-points, MMSE 20±1 and MMSE 17±1. We also calculated length-of-survival from reported time-of-disease-onset and from time-of-diagnosis, for each of the two diagnostic groups.

Kaplan-Meyer curves were constructed to show the survival distribution, while Log-rank tests were computed to compare survival between the two diagnostic groups.

Results

- The average length-of-survival for AD patients did not significantly differ from that of DLB patients when investigated from the reported time-of-disease-onset.

- When counted from time-of-diagnosis, DLB patients length-of-survival was significantly shorter compared to that of AD patients.

- No correlation was found between MMSE score and reported disease duration at the time of diagnosis, neither in the total cohort nor in AD and DLB groups, separately.

- Measured at the time of diagnosis, the median MMSE score and median length of time since onset were equal between AD and DLB patients. However the range in both variables was notable.

- From the time of MMSE 20±1 and from the time of MMSE 17±1, DLB patients had significantly shorter length-of-survival compared to AD patients.

- According to a multivariate cox regression analysis, dementia diagnosis influenced length-of-survival from time of diagnosis, and also when taken from the time the patient's MMSE score reached 17±1. Age was the sole independent variable that influenced length-of-survival from the time the patient's MMSE score reached 20±1.

Comments

The aim of this study was to test the hypothesis that a diagnosis of DLB implies a poorer prognosis compared to a diagnosis of AD. The objective is not new, but results in earlier studies have been inconsistent, which we argue is at least partly due to methodological shortcomings. This is supported in a recent review by Brodaty et al., who argue that the performance of a meta-analysis on survival in dementia is precluded by numerous study deficiencies [259]. We challenge what we consider the conventional strategy. In addition to measuring length-of-survival from the time of diagnosis, and from the time of disease onset, we compared time-to-death from predefined cognitive levels in order to increase the sensitivity of the measurements to detect differences.

We used MMSE [237] as a staging system. This scale was not specifically designed as a staging system, but it is currently widely used to evaluate cognitive ability, e.g. before inclusion in clinical trials, and to compare cognitive abilities in multiple groups. According to Kraemer et al. [270], MMSE can be adapted to perform as a staging system in AD, and in doing so, achieves high validity and reliability. Compared to other available staging systems, i.e. Global Deterioration Scale (GDS) [271], MMSE seems the better choice for tracking disease course in the earlier stages of AD; whereas with DLB, MMSE may lack sensitivity to detect cognitive deficits or changes over time, due in part to the different neuropsychological profiles, with more visual-perceptual and attentional deficits in DLB [272]. This implies that, the shorter length-of-survival seen in DLB, may reflect a greater disease severity at the selected time-points, MMSE 20±1 and MMSE 17±1, compared to AD patients at the same time-points.

For comparison we also investigated length-of-survival from reported time of disease onset and from the time of diagnosis. Brodaty et al. [259] noted that the time that the patients will say that symptoms began is an endorsement that is influenced by patient and caregiver sensitivity to symptoms, retrospective memory and what differing thresholds may be representative in culture and attitude. We suggest that the variable reported-duration-of-symptoms may be poorly reliable and lacking in validity. Therefore, the difference in survival-length from disease onset cannot be shown. Using the time-point, time of diagnosis, is also problematic. When the qualified diagnosis is made is influenced by health-seeking behavior, the healthcare system, as well as cultural and personal background. In our population, the MMSE score at the time of diagnosis ranged from 6-29, in other words from severely impaired to normally functioning. Despite this, we believe that using time-of-diagnosis is the more reliable strategy to rate the stage of disease, since it is the point when the patient has chosen to seek medical attendance. It is also a clinically relevant moment when a prognostic tool would be of great value.

5.3. Paper III

The hypothesis in Paper III was that concomitant autonomic dysfunction in dementia with Lewy bodies is associated with poorer prognosis.

Thirty patients with DLB and PDD were included in this prospective, three-year study. During the follow-up, each patient was assessed with orthostatic blood pressure measurements at baseline, 12 and 24 weeks. Blood pressure was recorded after at least 10 minutes of rest in supine position, again immediately after standing up, and then after one, three, five and ten minutes of standing. Thirty blood pressure readings were obtained for each patient.

With the intention to carefully grade the presence and severity of orthostatic hypotension, each systolic and diastolic blood pressure measurement was dichotomized into orthostatic or not orthostatic according to the classic definition –"… reduction in systolic blood pressure of at least 20 mmHg or a reduction of diastolic blood pressure of at least 10 mmHg" [273]. Persistent orthostatic hypotension was defined as at least 5 out of 30 orthostatic values, i.e. blood pressure readings that fell below criterion.

Somatic symptoms of urinary incontinence were detected as if the patient (or caregiver) endorsed these during a clinical interview based on the Disability Assessment for Dementia (DAD) scale [255]. The presence of constipation was defined out of regular use of purgatives and/or enemas.

Results

- Orthostatic hypotension was found in 25 (83%) out of the 30 patients and 15 (50%) had persistent orthostatic hypotension. Urinary incontinence and constipation were equally common (30%).

- Seven (23%) of the 30 patients died during the follow up.

- Patients with persistent orthostatic hypotension exhibited shorter survival duration compared to patients with no or only mild orthostatic hypotension (Log rank x^2=4.47, p=0.034).

- Patients were divided into three groups; Group 1 (n=15) included those with no or only mild orthostatic hypotension, Group 2 (n=7) had isolated and persistent orthostatic hypotension, and Group 3 (n=8) had persistent orthostatic hypotension together with constipation and/or urinary constipation. We found differences among the three groups, where patients in Group 3 had the shortest length-of-survival and Group 2 the next shortest (Log Rank x^2=6.370, p=0.041)

- The two patients with all three manifestations had the shortest survival.

Comments

Autonomic dysfunction in demented patients is usually a silent feature, meaning that symptoms are not always clear, and patients or caregivers may not always emphasize them themselves. Incontinence can be mistaken for practical difficulties to use the toilet. Constipation can easily be explained by immobility or a side-effect from drugs. Orthostatic hypotension may lack frank symptoms in as much as 43% of the cases in a non-demented cohort according to Arbogast et al. [274]. Passant et al. showed that, also among demented patients, few presented with typical symptoms of (objectively confirmed) orthostatic hypotension [275]. Our use of objective measures to identify orthostatic hypotension is therefore a strength of this study.

Even though autonomic dysfunction may be hard to detect by clinical interview, and is not spontaneously reported by patients or caregivers, it may have impact on life in several ways. In literature, there are reports of probable effects on quality of life [276,277,278,279], functional status [278], depression [280], cognition [281,282,283], and survival [284,285] in these patients. A recent study also proposed that autonomic dysfunction in patients with RBD may be a prodromal sign and a predictor of later development of Parkinson's disease or Dementia with Lewy bodies [286].

The study sample in this article is small, which brings statistical limitations as well as scientific. For example, multivariate analysis to adjust for possible confounders was not feasible, due to the small sample size and the low number of events during

follow-up. The strengths of the study are its prospective strategy, the relatively long follow-up time and the detailed methods used to evaluate orthostatic hypotension.

5.4. Paper IV

The hypothesis in Paper IV is based on our clinical observation that patients who respond to treatment seems to have a more benign clinical course. There are many possible explanations for this, but one is that treatment modifies disease in the sub-group of patients who respond to treatment. To our knowledge, there are no earlier studies addressed to the prognostic value of a positive treatment response in neurodegenerative dementia. Therefore, we set up this study to investigate length-of-survival in patients treated with memantine or placebo, where treatment response was evaluated by Clinical Global Assessment of Change (CGIC).

According to Chan and Holford [287], the effect of drug treatment in chronic neurodegenerative diseases can be symptomatic or protective. A positive response to a symptomatic drug would be improvement in clinically relevant symptoms, such as, for example, enhanced cognition, greater autonomy, or improvement in neuro-psychiatric and behavioral dysfunction. However, the symptomatic approach does not arrest the long term degenerative process. The withdrawal of a symptomatic drug is typically followed by the disappearance of the beneficial effects. In comparison, a protective or disease-modifying drug affects the underlying pathological process and changes the trajectory of the clinical course.

The RCTs using memantine in DLB/PDD populations included follow-up assessments at 22 to 24 weeks. Since the course of DLB, PDD and other dementias endures for several years, measurement at 22-24 weeks must be considered a short term follow-up, with the aim to assess potential symptomatic improvement. An extension study performed by Johansson et al. [288] included a 4-week wash-out, and 26-week, open-label treatment during a continuation phase of the RCT reported by Aarsland et al. [84]. They showed that recurrence of symptoms during the wash out occurred more often in the memantine treated group compared to the placebo group, which suggests a symptomatic effect of the drug.

We performed a 3-year follow-up on the Swedish population included in the Aarsland study. The outcome measure was length-of-survival, which we consider an indicator of a possible protective drug effect.

Results

- Patients who received memantine (n=18) instead of placebo (n=14) in the original RCT by Aarsland et al. [84] had a higher rate of survival at the 3-year follow-up (Log rank x^2=6.03, p=0.03).

- Patients who received and had a positive effect of memantine (n=12) lived longer compared to the non-responders (n=6) (Log rank x^2=6.595, p=0.010).

- No significant difference was found in length-of-survival between patients who had responded positively to placebo (n=9) and those who did not respond to treatment with placebo (n=5) in the original RCT (Log rank x^2= 0.161, p=0.689).

- Based on Clinical Global Assessment of Change (CGIC) [256] scores obtained at week 54, when all patients in the original placebo group had been placed in treatment with memantine for 24 weeks, no differences were found at the 3-years follow-up between responders and non-responders (Log rank x^2=1.834, p=0.176).

Comments

Finding a cure for dementia would be the ultimate goal, but to detect and verify any disease-modifying effect is difficult. Investigators have to consider the variances expected in the clinical course both within and between individuals. Furthermore, EMEA guidelines state that a true effect on the underlying pathology cannot be established on clinical data alone [289]. Reliable and valid biomarkers in direct association with the underlying disease process are needed, to accompany key clinical targets while potential effects are measured. In this thesis we refer to markers that are useful in assessing change due to treatment, as markers of progression or rate markers. To prove a disease modifying effect, a rate marker must be measured at least twice. We argue that our clinical outcome measure, length- of-survival, may be an indicator of a possible protective effect; but alone, it generates findings that are far from conclusive.

We divided memantine-treated patients into responders and non-responders. It would be of great interest to understand how the responders differ from non-responders, and to identify possible predictors of response. As suggested by Camicioli et al., there may be subgroups of patients within disease groups who may demonstrate treatment response [290]; or it might be that we must look beyond the diagnosis in order to target patients who will respond to treatment. For ChEI, one study reported that a subgroup of DLB patients with hallucinations showed a preferential response to treatment with rivastigmine [208]. Clinical trials on memantine in DLB/PDD populations are still in their infancy, and we have found no earlier studies addressing this issue.

In general, long-term follow-up studies are required to better understand the natural course of the neurodegenerative process and a validated biomarker program to detect subgroups of patients is needed. Subgroups may be identifyed based on differences in clinical features or neuropathological mechanisms. For example, the clinical and neuropathological overlap between DLB and AD must be taken into consideration in clinical trials and response to treatment may differ along the clinico-pathological continuum of AD-DLB/PDD-PD. To check for differences in diagnostic accuracy between memantine- and placebo-treated patients, and between responders and non-responders in the memantine-treated group, we used 2 different strategies (Table 6). The first, was one proposed by Palmqvist et al. [245], in which we applied an algorithm (MMSE orientation x 3 ≥ the total MMSE scores) to differentiate DLB from AD. In our sample, 28 (88%) out of 32 patients fulfilled this "DLB criterion" and they were equally distributed in the two groups. For the second, we followed Fujishiro et al. [291], who, in order to validate the pathologic criteria of the Third Consortium on Dementia with Lewy bodies, counted the number of core clinical features and RBD in prospectively followed DLB and AD patients. They found that the number of core clinical features and RBD correlated with the likelihood of DLB pathology at autopsy. As in Fujishiro et al., we extracted information on core clinical features and RBD for each patient, utilizing the following scales: NPI [292](for visual hallucinations), UPDRS (for extrapyramidal symptoms), Mayo Fluctuation Scale (MFS) [293] (for fluctuation in alertness/cognition) and Stavanger Sleep Questionnaire (SSQ)[294] (for RBD). Each symptom was dichotomized into present or not present and the number of present core features and RBD was added (maximum 4). No significant differences in the number of core symptoms and RBD were found between responders and non-responders. We also applied these two strategies to check for differences between the patients who received memantine and placebo during the original RCT. No differences in distribution of AD suspected features were found.

Table 6. Computing on the likelihood of DLB diagnosis.

	Memantine group (n=18)			Total study population (n=32)		
	Responders (n=12)	Non-responders (n=6)	p	Memantine (n=18)	Placebo (n=14)	p
Number of patients with MMSE orientation score x 3 ≥ total MMSE score	10 (83%)	5 (83%)	ns	15 (83%)	13 (93%)	ns
Number of core symptoms + RBD (max 4) median (range)	3 (1-4)	3 (2-4)	ns	3 (1-4)	3 (1-4)	ns

Table 6 shows results that indicate diagnostic accuracy in our sample. Moreover, the lack of differences between groups indicates that the longer survival seen in

memantine-responders vs non-responders and memantine-group vs placebo-group may not be explained by concomitant AD pathology.

6. General Comments

6.1. The objectives

The aim in this thesis is to search for markers that predict either a more aggressive clinical course or a shorter time to death in patients with a known clinical diagnosis of AD or DLB/PDD. From our point of view such markers may function as *state markers*, in that these identify subgroups of patients within or outside selected diagnostic groups; *stage markers,* which indicate stages during the course of disease (e.g. early, advanced etc.); or *rate markers*, which indicate the rate of progression through stages (see Figure 1 on page 30-31). The biomarkers we have chosen to study are already well established clinical variables, though this thesis considers these with potentially new roles. The biomarkers used in this thesis were chosen based on our clinical observations.

Rate markers, as indicators of the rate of progression through disease stages are needed to detect true treatment effects of disease modifying drugs, such that the disease progression would slow down or halt with effective treatment. Such markers should, among other things, be in direct association with the underlying pathological process and be generalizable to people fitting many different characteristics, including gender, age, level of education etc. [295]. Clinical test results based on cognitive and functional performance, or quality of life cannot discriminate true disease modification from symptomatic treatment effects. Rate markers fall within the scope for this thesis since they also provide prognostic information.

Biomarkers that predict conversion from preclinical and prodromal stages to dementia stage/ major neurocognitive disorder are not in the scope for this thesis. In the case of AD, such markers serve as diagnostic *state markers*. As potentially disease-modifying treatments become available, sensitive tools to identify AD patients already in the earliest stages are needed, so that treatment is initiated as soon as possible. Furthermore, given a high diagnostic accuracy in clinical trials, subtle effects from medication on the underlying disease process would be easier to detect.

The establishment of reliable prognostic markers could help us to

- describe the natural course of the neurodegenerative process

- identify factors that influence the rate of disease progression

- identify subgroups of patients

- identify patients at risk for rapid deterioration.

- detect disease-modifying effects from treatment

6.2. The study sample

The participants in the studies were selected from samples recruited for larger follow-up studies conducted in the Malmö Memory Clinic. All patients reported on in Papers I-II were referred to the clinic as a part of clinical routine, while some patients reported on in Papers III-IV were specifically recruited from other psychiatry or neurology outpatient clinics. For the AD patients included in our studies, there is a possible selection bias. For instance, in Sweden many patients with AD are successfully managed in primary care and may never be referred to a specialist clinic. For the DLB patients, our samples may be more representative since most of the DLB patients in Sweden are attended by a specialist. However, all AD patients in this thesis were originally included in SATS, a study designed with wide inclusion criteria, which accepted coexisting illnesses and concomitant medications. This created a more clinically realistic sample compared to many other clinical trials. The structured management of all original study populations provided qualitative strength to this thesis. All patients fulfilled well-established diagnostic criteria at baseline and diagnosis was continuously evaluated during the prospective follow-up. In all original follow-up studies, one of the inclusion criteria was mild-to-moderate dementia, which happens to be the clinical phase when cognitive test scores are most reliable. Almost all patients were being administered cholinesterase inhibitors, which in all papers this was considered a baseline characteristic, and when applicable (in Paper II), included in a multivariate cox regression analysis.

6.3. The findings

For Paper I we explored the potential role of CSF T-tau in AD. Earlier research had already established that moderately elevated T-tau, together with elevated P-tau and low Aß, are diagnostic markers of AD, and therefore, this biomarker pattern is an AD state marker. The idea of using biomarkers obtained from CSF to understand and describe the clinical course of dementia is not new, but our study contributes to this knowledge by proposing the additional roles of T-tau as a rate marker and maybe also an AD subgroup state marker. The basis for this is that high T-tau is associated with a faster rate of decline in MMSE score, though not ADAS-Cog,

over time, and patients with high T-tau have a deviating profile on cognitive tests. Furthermore, high T-tau levels are also associated with lower cognitive performance scores on MMSE and ADAS-Cog at baseline, and hence, in our study, T-tau behaves as a stage marker. However, this must be considered less likely, as T-tau levels are believed to remain stable over time in AD patients. We conclude that P-tau appears to serve as a stage marker as well, but not a rate marker, even though P-tau and T-tau levels are correlated in this population. As a stage- or rate-marker, Aß42 was a poor indicator in this study.

The diagnostic type of dementia was related to prognosis (Paper II). Based on our results, we propose that a diagnosis of DLB indicates a state that is associated with a poorer prognosis when compared to the diagnosis of AD. However, we chose to measure survival length from distinct time-points associated with a cognitive performance score on the MMSE, and it can also be that DLB patients at these time-points are at more advanced stages in the course of disease and consequently have a shorter time to death.

Presence of severe autonomic dysfunction was also associated with a poorer prognosis (Paper III). It may be that there is a subgroup of dementia patients who suffer from severe dysautonomia, which in that case could be used as a state marker to indicate patients with a poorer prognosis. It can also be that autonomic dysfunction is a progressive clinical feature that increases over time in all DLB/PDD patients and that a patient with severe autonomic dysfunction simply has reached an advanced stage in the DLB disease course. If so, it is a stage marker identifying patients who will have a shorter timespan to death compared to patients without severe dysautonomia.

Our findings in Paper IV indicate that a good response to early treatment with memantine in DLB/PDD patients predicts a better prognosis. Can this be explained by a susceptibility to treatment in patients at earlier stages of the disease? Or, is a positive response to treatment a state marker for a distinctly different diagnostic subtype of disease, with which memantine may hold particular therapeutic benefit? We hope that future research can find the answers to these questions.

6.4. Future research

Many earlier studies on potential prognostic markers for dementia, whether for state, stage or rate of progression indicators, could be criticized for methodological shortcomings and reviews fail to establish reliable prognostic markers. Several methodological improvements are recommended for future research, including larger sample sizes (>100 patients [129]), longer follow-up, more appropriate statistics, more clearly defined terminology and a more thorough selection and characteriza-

tion of study samples. Some of these recommendations are, however, difficult to achieve, partly due to the malignant course and the fragility of dementia patients.

The phenotype of dementia must be influenced by the interplay of genetic, biological, physical, psychological, social and environmental factors. A tool for prediction of prognosis may be dependent on disease stage or only applicable in specific subgroups of dementia patients. Even with reliable prognostic markers in the future, no statistical model can ever be able to predict unforeseen events like medical illnesses or medication-induced delirium.

7. Conclusions

7.1. General conclusion

This thesis adds to current knowledge about predicting prognosis in neurodegenerative dementia by reporting on studies investigating potential biomarkers that predict more rapid deterioration or a shorter length-of-survival. We have found that already well-established clinical variables also may provide prognostic information. The prospective design and the well-structured clinical follow-up in our studies, as reported in the four papers, are strengths in this thesis. However, our findings are preliminary and must be confirmed in future research with larger study samples, allowing a more appropriate statistical approach.

7.2. Specific conclusions

Paper I

The results in Paper I indicate that very high T-tau concentration levels in CSF have clinical implications. High levels may imply a more intense neuronal degeneration. HighT-tau levels may also identify a possible subtype of AD dementia in our sample of patients, who present differently, with greater performance deficits on cognitive tests and a particularly pronounced AD profile on cognitive tests compared to patients with relatively lower T-tau levels.

Paper II

Our findings suggest that patients with DLB have a shorter length-of-survival from the time of diagnosis, from the time of MMSE 20±1 and from the time of MMSE 17±1. These findings underscore the great importance of accurate diagnosis and the need for early support for DLB patients and their families.

Paper III

A high frequency of autonomic dysfunction was found in our population of patients with DLB and PDD. Even though our study sample was small, the findings indicate that the presence and severity of autonomic dysfunction may have impact on survival length. Since orthostatic hypotension seems to be the most clinically important feature in these patients, associated with no or atypical symptoms, we recommend orthostatic blood pressure measurement in all patients with DLB/PDD.

Paper IV

This study examined the effect of early treatment with memantine on survival in DLB/PDD patients. Our results indicate that patients who respond positively to such early treatment will on average live longer. Due to the limitations following a small sample size, and a possible bias effect from subgroup analysis, our findings are not conclusive. We cannot propose a disease modifying effect from memantine, but nevertheless, we hope to inspire to future research on this issue.

8. Acknowledgements

I wish to express my warmest gratitude to all the persons who had contributed to this thesis. My special and most sincere thanks to:

EIisabet Londos. I know I am privileged to have had you as my supervisor. You have introduced me to the world of science with great care and a sure instinct. You have generously shared your knowledge and experience, and your true dedication to help people with dementia is inspiring. Looking back as this thesis is finished, I hope we shall see this was just the beginning of our friendship!

My co-supervisor, **Lennart Minthon**. You know how to grow peaches and how to refurbish old windows. You also know how to create a prosperous research unit and how to bring people to enjoy going to work. I know no one like you! Thank you, for making this possible and for always supporting me.

My co-authors, **Henrik Zetterberg, Kaj Blennow, Oskar Hansson, Dag Aarsland and Clive Ballard.** You are all experienced and well –merited researchers, and it has been an honor to work with you. Thank you for valuable contribution to the manuscripts and for your scientific guidance!

All the members of the research group, for inspiring meetings and friendly companionship. I especially want to thank: My friend, **Gustav Torisson**, we started medical school together, and later on were both caught up by the enthusiastic Doctor Londos. Thank you for the many worthwhile talks about science and life – and for figure preparation; **Victoria Larsson**, for excellent cooperation on Paper IV, linguistic support every now and then, and for those amusing moments whenever we meet; **Carina Wattmo**, for statistical guidance and for generously sharing pieces of advice from your own thesis-preparation; **Sebastian Palmqvist**, for clever scientific input and being the perfect lead on the dancefloor! **Erik Stomrud**, for your enthusiastic commitment to the research group, and for refreshing debates during the lunch-breaks.

All co-workers at the Memory Clinic, especially **Eva Falk-Langebro,** for sharing your clinical skills in the care of patients with dementia with Lewy bodies, and, **Agneta Nilsson,** for making my work easier and less stressful.

The helpful **staff at the Medical Faculty Library,** especially **Jan Jensen,** who with great calmness helped me to get along with EndNote.

The **staff at the Customer Service, Lärcenter Falköping**, for efficient service, and **Yvonne Fällström,** for your company and nice small talk.

Kevin Grimes, for your editorial suggestions on my kappa!

All **my collegues at the Unit of Rheumatology at Skaraborgs Sjukhus,** for your patience during the time that I was finishing this thesis. You have showed great flexibility, which made it all possible.

Johann's family. Even though you live far away, your role in this work has been important! I appreciate your genuine support and the love you always show me.

Mamma, Pappa, Viktor and Stina, for your unconditional love. What you have given me have been the prerequisite for me to achieve this and other goals. You have taught me that life is meant to be shared and you are, forever, my safest harbor.

My deeply beloved husband, **Johann**. It was our mutual decision that I should finish this thesis, and you never doubted I would complete it. I am proud we made it! You are a clever scientist, and our creative discussions have inspired and helped me a lot. Thank you for being such a wonderful friend. Dance me to the end of love!

Hanna, for never letting me get away from you!

9. References

1. World Health Organisation. (1992) The ICD-10. International Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva, Switzerland: World Health Organisation.

2. American Psychiatric Association. (1994) Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition (DSM-IV). Washington D.C.: American Psychiatric Association.

3. American Psychiatric Association. (2013) Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Washington, DC: American Psychiatric Association.

4. Blazer D (2013) Neurocognitive disorders in DSM-5. The American journal of psychiatry 170: 585-587.

5. Kurz AF, Lautenschlager NT (2010) The concept of dementia: retain, reframe, rename or replace? International psychogeriatrics / IPA 22: 37-42.

6. McKhann G, Drachman D, Folstein M, Katzman R, Price D, et al. (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34: 939-944.

7. Blacker D, Albert MS, Bassett SS, Go RC, Harrell LE, et al. (1994) Reliability and validity of NINCDS-ADRDA criteria for Alzheimer's disease. The National Institute of Mental Health Genetics Initiative. Archives of neurology 51: 1198-1204.

8. Dewan MJ, Gupta S (1992) Toward a definite diagnosis of Alzheimer's disease. Comprehensive psychiatry 33: 282-290.

9. Jobst KA, Barnetson LP, Shepstone BJ (1998) Accurate prediction of histologically confirmed Alzheimer's disease and the differential diagnosis of dementia: the use of NINCDS-ADRDA and DSM-III-R criteria, SPECT, X-ray CT, and Apo E4 in medial temporal lobe dementias. Oxford Project to Investigate Memory and Aging. International psychogeriatrics / IPA 10: 271-302.

10. Kukull WA, Larson EB, Reifler BV, Lampe TH, Yerby MS, et al. (1990) The validity of 3 clinical diagnostic criteria for Alzheimer's disease. Neurology 40: 1364-1369.

11. Kazee AM, Eskin TA, Lapham LW, Gabriel KR, McDaniel KD, et al. (1993) Clinicopathologic correlates in Alzheimer disease: assessment of clinical and pathologic diagnostic criteria. Alzheimer disease and associated disorders 7: 152-164.

12. Lim A, Tsuang D, Kukull W, Nochlin D, Leverenz J, et al. (1999) Clinico-neuropathological correlation of Alzheimer's disease in a community-based case series. Journal of the American Geriatrics Society 47: 564-569.

13. Varma AR, Snowden JS, Lloyd JJ, Talbot PR, Mann DM, et al. (1999) Evaluation of the NINCDS-ADRDA criteria in the differentiation of Alzheimer's disease and frontotemporal dementia. Journal of neurology, neurosurgery, and psychiatry 66: 184-188.

14. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, et al. (2007) Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet neurology 6: 734-746.

15. Jack CR, Jr., Albert MS, Knopman DS, McKhann GM, Sperling RA, et al. (2011) Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 7: 257-262.

16. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Jr., et al. (2011) The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 7: 263-269.

17. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, et al. (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 7: 270-279.

18. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, et al. (2011) Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 7: 280-292.

19. Moller HJ, Graeber MB (1998) The case described by Alois Alzheimer in 1911. Historical and conceptual perspectives based on the clinical record and neurohistological sections. European archives of psychiatry and clinical neuroscience 248: 111-122.

20. Crystal H, Dickson D, Fuld P, Masur D, Scott R, et al. (1988) Clinico-pathologic studies in dementia: nondemented subjects with pathologically confirmed Alzheimer's disease. Neurology 38: 1682-1687.

21. Jack CR, Jr., Knopman DS, Jagust WJ, Shaw LM, Aisen PS, et al. (2010) Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet neurology 9: 119-128.

22. Price JL, Morris JC (1999) Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Annals of neurology 45: 358-368.

23. Mortimer AM, Likeman M, Lewis TT (2013) Neuroimaging in dementia: a practical guide. Practical neurology 13: 92-103.

24. Haass C, Schlossmacher MG, Hung AY, Vigo-Pelfrey C, Mellon A, et al. (1992) Amyloid beta-peptide is produced by cultured cells during normal metabolism. Nature 359: 322-325.

25. Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 297: 353-356.

26. Roher AE, Palmer KC, Yurewicz EC, Ball MJ, Greenberg BD (1993) Morphological and biochemical analyses of amyloid plaque core proteins purified from Alzheimer disease brain tissue. Journal of neurochemistry 61: 1916-1926.

27. Miller DL, Papayannopoulos IA, Styles J, Bobin SA, Lin YY, et al. (1993) Peptide compositions of the cerebrovascular and senile plaque core amyloid deposits of Alzheimer's disease. Archives of biochemistry and biophysics 301: 41-52.

28. Jarrett JT, Berger EP, Lansbury PT, Jr. (1993) The carboxy terminus of the beta amyloid protein is critical for the seeding of amyloid formation: implications for the pathogenesis of Alzheimer's disease. Biochemistry 32: 4693-4697.

29. Walsh DM, Selkoe DJ (2004) Deciphering the molecular basis of memory failure in Alzheimer's disease. Neuron 44: 181-193.

30. Blennow K, de Leon MJ, Zetterberg H (2006) Alzheimer's disease. Lancet 368: 387-403.

31. Grundke-Iqbal I, Iqbal K, Tung YC, Quinlan M, Wisniewski HM, et al. (1986) Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. Proceedings of the National Academy of Sciences of the United States of America 83: 4913-4917.

32. Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K (2006) Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta neuropathologica 112: 389-404.

33. Braak H, Braak E (1991) Neuropathological stageing of Alzheimer-related changes. Acta neuropathologica 82: 239-259.

34. Blessed G, Tomlinson BE, Roth M (1968) The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. The British journal of psychiatry : the journal of mental science 114: 797-811.

35. Nelson PT, Alafuzoff I, Bigio EH, Bouras C, Braak H, et al. (2012) Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. Journal of neuropathology and experimental neurology 71: 362-381.

36. Querfurth HW, LaFerla FM (2010) Alzheimer's disease. The New England journal of medicine 362: 329-344.

37. Arendt T (2009) Synaptic degeneration in Alzheimer's disease. Acta neuropathologica 118: 167-179.

38. Bowen DM, Smith CB, White P, Davison AN (1976) Neurotransmitter-related enzymes and indices of hypoxia in senile dementia and other abiotrophies. Brain : a journal of neurology 99: 459-496.

39. Whitehouse PJ, Price DL, Clark AW, Coyle JT, DeLong MR (1981) Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. Annals of neurology 10: 122-126.

40. Birks J (2006) Cholinesterase inhibitors for Alzheimer's disease. The Cochrane database of systematic reviews: CD005593.

41. Koh JY, Yang LL, Cotman CW (1990) Beta-amyloid protein increases the vulnerability of cultured cortical neurons to excitotoxic damage. Brain research 533: 315-320.

42. Harkany T, Abraham I, Timmerman W, Laskay G, Toth B, et al. (2000) beta-amyloid neurotoxicity is mediated by a glutamate-triggered excitotoxic cascade in rat nucleus basalis. The European journal of neuroscience 12: 2735-2745.

43. Thomas SJ, Grossberg GT (2009) Memantine: a review of studies into its safety and efficacy in treating Alzheimer's disease and other dementias. Clinical interventions in aging 4: 367-377.

44. Wilcock GK (2003) Memantine for the treatment of dementia. Lancet neurology 2: 503-505.

45. Areosa SA, Sherriff F, McShane R (2005) Memantine for dementia. The Cochrane database of systematic reviews: CD003154.

46. Citron M (2010) Alzheimer's disease: strategies for disease modification. Nature reviews Drug discovery 9: 387-398.

47. Kosaka K, Yoshimura M, Ikeda K, Budka H (1984) Diffuse type of Lewy body disease: progressive dementia with abundant cortical Lewy bodies and senile changes of varying degree--a new disease? Clinical neuropathology 3: 185-192.

48. Perry RH, Irving D, Blessed G, Perry EK, Fairbairn AF (1989) Clinically and neuropathologically distinct form of dementia in the elderly. Lancet 1: 166.

49. Hansen L, Salmon D, Galasko D, Masliah E, Katzman R, et al. (1990) The Lewy body variant of Alzheimer's disease: a clinical and pathologic entity. Neurology 40: 1-8.

50. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, et al. (1996) Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 47: 1113-1124.

51. Litvan I, Bhatia KP, Burn DJ, Goetz CG, Lang AE, et al. (2003) Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. Movement disorders : official journal of the Movement Disorder Society 18: 467-486.

52. McKeith I, Mintzer J, Aarsland D, Burn D, Chiu H, et al. (2004) Dementia with Lewy bodies. Lancet neurology 3: 19-28.

53. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, et al. (2005) Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 65: 1863-1872.

54. Lewy F (1912) Paralysis Agitans Part I: Patologische Anatomie. Lewandowsky Med Handbuch der Neurologie. Berlin: Springer. pp. 920-933.

55. Tretiakoff C (1919) Contribution à l'étude de l'anatomie du locus niger de Soemmering avec quelques déductions relatives à la pathogénie des troubles du tonus musculaires et de la maladie de Parkinson. Thèse de Paris.

56. Holdorff B (2002) Friedrich Heinrich Lewy (1885-1950) and his work. Journal of the history of the neurosciences 11: 19-28.

57. Jellinger KA (2007) Morphological substrates of parkinsonism with and without dementia: a retrospective clinico-pathological study. Journal of neural transmission Supplementum: 91-104.

58. Jellinger KA (2009) Formation and development of Lewy pathology: a critical update. Journal of neurology 256 Suppl 3: 270-279.

59. Braak H, Del Tredici K (2008) Invited Article: Nervous system pathology in sporadic Parkinson disease. Neurology 70: 1916-1925.

60. Halliday GM, Holton JL, Revesz T, Dickson DW (2011) Neuropathology underlying clinical variability in patients with synucleinopathies. Acta neuropathologica 122: 187-204.

61. Rockenstein E, Hansen LA, Mallory M, Trojanowski JQ, Galasko D, et al. (2001) Altered expression of the synuclein family mRNA in Lewy body and Alzheimer's disease. Brain research 914: 48-56.

62. Lippa CF, Duda JE, Grossman M, Hurtig HI, Aarsland D, et al. (2007) DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. Neurology 68: 812-819.

63. Samuel W, Galasko D, Masliah E, Hansen LA (1996) Neocortical lewy body counts correlate with dementia in the Lewy body variant of Alzheimer's disease. Journal of neuropathology and experimental neurology 55: 44-52.

64. Hurtig HI, Trojanowski JQ, Galvin J, Ewbank D, Schmidt ML, et al. (2000) Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. Neurology 54: 1916-1921.

65. Aarsland D, Perry R, Brown A, Larsen JP, Ballard C (2005) Neuropathology of dementia in Parkinson's disease: a prospective, community-based study. Annals of neurology 58: 773-776.

66. Harding AJ, Halliday GM (2001) Cortical Lewy body pathology in the diagnosis of dementia. Acta neuropathologica 102: 355-363.

67. Hughes AJ, Daniel SE, Blankson S, Lees AJ (1993) A clinicopathologic study of 100 cases of Parkinson's disease. Archives of neurology 50: 140-148.

68. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, et al. (2003) Staging of brain pathology related to sporadic Parkinson's disease. Neurobiology of aging 24: 197-211.

69. Harding AJ, Broe GA, Halliday GM (2002) Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. Brain : a journal of neurology 125: 391-403.

70. Kovari E, Horvath J, Bouras C (2009) Neuropathology of Lewy body disorders. Brain research bulletin 80: 203-210.

71. Gomez-Tortosa E, Newell K, Irizarry MC, Albert M, Growdon JH, et al. (1999) Clinical and quantitative pathologic correlates of dementia with Lewy bodies. Neurology 53: 1284-1291.

72. Perry EK PM, Johnson M et al (2003) Neurotransmitter correlates of neuropsychiatric symptoms in dementia with Lewy bodies. In: Bedard M-A AY, Chourinard S, Fahn S, Korczyn AD, Lesperance P editor. Mental and dehavioural dysfunction in movement disorders. Totowa, NJ: Humana Press INc. pp. 285-294.

73. Aarsland D, Ballard CG, Halliday G (2004) Are Parkinson's disease with dementia and dementia with Lewy bodies the same entity? Journal of geriatric psychiatry and neurology 17: 137-145.

74. Merdes AR, Hansen LA, Jeste DV, Galasko D, Hofstetter CR, et al. (2003) Influence of Alzheimer pathology on clinical diagnostic accuracy in dementia with Lewy bodies. Neurology 60: 1586-1590.

75. Del Ser T, Hachinski V, Merskey H, Munoz DG (2001) Clinical and pathologic features of two groups of patients with dementia with Lewy bodies: effect of coexisting Alzheimer-type lesion load. Alzheimer disease and associated disorders 15: 31-44.

76. Edison P, Rowe CC, Rinne JO, Ng S, Ahmed I, et al. (2008) Amyloid load in Parkinson's disease dementia and Lewy body dementia measured with [11C]PIB positron emission tomography. Journal of neurology, neurosurgery, and psychiatry 79: 1331-1338.

77. Jokinen P, Scheinin N, Aalto S, Nagren K, Savisto N, et al. (2010) [(11C]PIB-, [(18)F]FDG-PET and MRI imaging in patients with Parkinson's disease with and without dementia. Parkinsonism & related disorders 16: 666-670.

78. Kantarci K, Lowe VJ, Boeve BF, Weigand SD, Senjem ML, et al. (2012) Multimodality imaging characteristics of dementia with Lewy bodies. Neurobiology of aging 33: 2091-2105.

79. Ballard C, Kahn Z, Corbett A (2011) Treatment of dementia with Lewy bodies and Parkinson's disease dementia. Drugs & aging 28: 769-777.

80. Bohnen NI, Kaufer DI, Ivanco LS, Lopresti B, Koeppe RA, et al. (2003) Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. Archives of neurology 60: 1745-1748.

81. Bohnen NI, Kaufer DI, Hendrickson R, Ivanco LS, Lopresti BJ, et al. (2006) Cognitive correlates of cortical cholinergic denervation in Parkinson's disease and parkinsonian dementia. Journal of neurology 253: 242-247.

82. Rolinski M, Fox C, Maidment I, McShane R (2012) Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. The Cochrane database of systematic reviews 3: CD006504.

83. Dalfo E, Albasanz JL, Martin M, Ferrer I (2004) Abnormal metabotropic glutamate receptor expression and signaling in the cerebral cortex in diffuse Lewy body disease is associated with irregular alpha-synuclein/phospholipase C (PLCbeta1) interactions. Brain pathology 14: 388-398.

84. Aarsland D, Ballard C, Walker Z, Bostrom F, Alves G, et al. (2009) Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial. Lancet neurology 8: 613-618.

85. Emre M, Tsolaki M, Bonuccelli U, Destee A, Tolosa E, et al. (2010) Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial. Lancet neurology 9: 969-977.

86. Leroi I, Overshott R, Byrne EJ, Daniel E, Burns A (2009) Randomized controlled trial of memantine in dementia associated with Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 24: 1217-1221.

87. Ondo WG, Shinawi L, Davidson A, Lai D (2011) Memantine for non-motor features of Parkinson's disease: a double-blind placebo controlled exploratory pilot trial. Parkinsonism & related disorders 17: 156-159.

88. Larsson V, Aarsland D, Ballard C, Minthon L, Londos E (2010) The effect of memantine on sleep behaviour in dementia with Lewy bodies and Parkinson's disease dementia. International journal of geriatric psychiatry 25: 1030-1038.

89. Larsson V, Engedal K, Aarsland D, Wattmo C, Minthon L, et al. (2011) Quality of life and the effect of memantine in dementia with lewy bodies and Parkinson's disease dementia. Dementia and geriatric cognitive disorders 32: 227-234.

90. Kehagia AA, Barker RA, Robbins TW (2010) Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. Lancet neurology 9: 1200-1213.

91. Aarsland D, Ballard C, Rongve A, Broadstock M, Svenningsson P (2012) Clinical trials of dementia with Lewy bodies and Parkinson's disease dementia. Current neurology and neuroscience reports 12: 492-501.

92. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, et al. (2013) The global prevalence of dementia: a systematic review and metaanalysis. Alzheimer's & dementia : the journal of the Alzheimer's Association 9: 63-75 e62.

93. Wimo A, editor (2007) Demenssjukdomarnas samhällskostnader och antalet dementa i Sverige 2005. Stockholm: Socialstyrelsen. 47 p.

94. Rahkonen T, Eloniemi-Sulkava U, Rissanen S, Vatanen A, Viramo P, et al. (2003) Dementia with Lewy bodies according to the consensus criteria in a general population aged 75 years or older. Journal of neurology, neurosurgery, and psychiatry 74: 720-724.

95. Aarsland D, Zaccai J, Brayne C (2005) A systematic review of prevalence studies of dementia in Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 20: 1255-1263.

96. Saunders AM, Strittmatter WJ, Schmechel D, George-Hyslop PH, Pericak-Vance MA, et al. (1993) Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurology 43: 1467-1472.

97. Selkoe DJ, Podlisny MB (2002) Deciphering the genetic basis of Alzheimer's disease. Annual review of genomics and human genetics 3: 67-99.

98. Qiu C, von Strauss E, Fastbom J, Winblad B, Fratiglioni L (2003) Low blood pressure and risk of dementia in the Kungsholmen project: a 6-year follow-up study. Archives of neurology 60: 223-228.

99. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, et al. (2001) Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ 322: 1447-1451.

100. Qiu C, von Strauss E, Winblad B, Fratiglioni L (2004) Decline in blood pressure over time and risk of dementia: a longitudinal study from the Kungsholmen project. Stroke; a journal of cerebral circulation 35: 1810-1815.

101. Ruitenberg A, Skoog I, Ott A, Aevarsson O, Witteman JC, et al. (2001) Blood pressure and risk of dementia: results from the Rotterdam study and the Gothenburg H-70 Study. Dementia and geriatric cognitive disorders 12: 33-39.

102. Notkola IL, Sulkava R, Pekkanen J, Erkinjuntti T, Ehnholm C, et al. (1998) Serum total cholesterol, apolipoprotein E epsilon 4 allele, and Alzheimer's disease. Neuroepidemiology 17: 14-20.

103. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, et al. (2002) Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Annals of internal medicine 137: 149-155.

104. Almeida OP, Hulse GK, Lawrence D, Flicker L (2002) Smoking as a risk factor for Alzheimer's disease: contrasting evidence from a systematic review of case-control and cohort studies. Addiction 97: 15-28.

105. Patterson C, Feightner J, Garcia A, MacKnight C (2007) General risk factors for dementia: a systematic evidence review. Alzheimer's & dementia : the journal of the Alzheimer's Association 3: 341-347.

106. Peters R, Peters J, Warner J, Beckett N, Bulpitt C (2008) Alcohol, dementia and cognitive decline in the elderly: a systematic review. Age and ageing 37: 505-512.

107. Flicker L (2009) Life style interventions to reduce the risk of dementia. Maturitas 63: 319-322.

108. Wimo A, Winblad B, Jonsson L (2010) The worldwide societal costs of dementia: Estimates for 2009. Alzheimer's & dementia : the journal of the Alzheimer's Association 6: 98-103.

109. Maurer K, Volk S, Gerbaldo H (1997) Auguste D and Alzheimer's disease. Lancet 349: 1546-1549.

110. Steeman E, de Casterle BD, Godderis J, Grypdonck M (2006) Living with early-stage dementia: a review of qualitative studies. Journal of advanced nursing 54: 722-738.

111. Connell CM, Janevic MR, Gallant MP (2001) The costs of caring: impact of dementia on family caregivers. Journal of geriatric psychiatry and neurology 14: 179-187.

112. Wagner EH, Austin BT, Davis C, Hindmarsh M, Schaefer J, et al. (2001) Improving chronic illness care: translating evidence into action. Health affairs 20: 64-78.

113. Fox N GJ (2004) Biomarkers and surrogates. NeuroRx 1: 181.

114. Panza F, Solfrizzi V, Frisardi V, Maggi S, Sancarlo D, et al. (2011) Different models of frailty in predementia and dementia syndromes. The journal of nutrition, health & aging 15: 711-719.

115. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, et al. (2001) Frailty in older adults: evidence for a phenotype. The journals of gerontology Series A, Biological sciences and medical sciences 56: M146-156.

116. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Stone KL, et al. (2007) Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. The journals of gerontology Series A, Biological sciences and medical sciences 62: 744-751.

117. Baptista G, Dupuy AM, Jaussent A, Durant R, Ventura E, et al. (2012) Low-grade chronic inflammation and superoxide anion production by NADPH oxidase are the main determinants of physical frailty in older adults. Free radical research 46: 1108-1114.

118. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Cumming RG, et al. (2012) High-risk prescribing and incidence of frailty among older community-dwelling men. Clinical pharmacology and therapeutics 91: 521-528.

119. Bartali B, Frongillo EA, Bandinelli S, Lauretani F, Semba RD, et al. (2006) Low nutrient intake is an essential component of frailty in older persons. The journals of gerontology Series A, Biological sciences and medical sciences 61: 589-593.

120. Cawthon PM, Ensrud KE, Laughlin GA, Cauley JA, Dam TT, et al. (2009) Sex hormones and frailty in older men: the osteoporotic fractures in men (MrOS) study. The Journal of clinical endocrinology and metabolism 94: 3806-3815.

121. Afilalo J, Karunananthan S, Eisenberg MJ, Alexander KP, Bergman H (2009) Role of frailty in patients with cardiovascular disease. The American journal of cardiology 103: 1616-1621.

122. Ostir GV, Ottenbacher KJ, Markides KS (2004) Onset of frailty in older adults and the protective role of positive affect. Psychology and aging 19: 402-408.

123. Kulmala J, Nykanen I, Manty M, Hartikainen S (2013) Association between Frailty and Dementia: A Population-Based Study. Gerontology.

124. Buchman AS, Schneider JA, Leurgans S, Bennett DA (2008) Physical frailty in older persons is associated with Alzheimer disease pathology. Neurology 71: 499-504.

125. Fick DM, Agostini JV, Inouye SK (2002) Delirium superimposed on dementia: a systematic review. Journal of the American Geriatrics Society 50: 1723-1732.

126. Fick D, Foreman M (2000) Consequences of not recognizing delirium superimposed on dementia in hospitalized elderly individuals. Journal of gerontological nursing 26: 30-40.

127. Santangelo A, Testai M, Albani S, Mamazza G, Pavano S, et al. (2010) The clinical and rehabilitative complexity in dementia with Lewy bodies (DLB): experience on a random sample of elderly patients dwelling in an RSA ("Residenza Sanitaria Assistita") of Catania. Archives of gerontology and geriatrics 51: e7-10.

128. Ashford JW, Schmitt FA (2001) Modeling the time-course of Alzheimer dementia. Current psychiatry reports 3: 20-28.

129. Galasko DR, Gould RL, Abramson IS, Salmon DP (2000) Measuring cognitive change in a cohort of patients with Alzheimer's disease. Statistics in medicine 19: 1421-1432.

130. Mann UM, Mohr E, Gearing M, Chase TN (1992) Heterogeneity in Alzheimer's disease: progression rate segregated by distinct neuropsychological and cerebral metabolic profiles. Journal of neurology, neurosurgery, and psychiatry 55: 956-959.

131. Gauthier S, Vellas B, Farlow M, Burn D (2006) Aggressive course of disease in dementia. Alzheimer's & dementia : the journal of the Alzheimer's Association 2: 210-217.

132. Thalhauser CJ, Komarova NL (2012) Alzheimer's disease: rapid and slow progression. Journal of the Royal Society, Interface / the Royal Society 9: 119-126.

133. Iqbal K, Flory M, Khatoon S, Soininen H, Pirttila T, et al. (2005) Subgroups of Alzheimer's disease based on cerebrospinal fluid molecular markers. Annals of neurology 58: 748-757.

134. Iqbal K, Flory M, Soininen H (2013) Clinical symptoms and symptom signatures of Alzheimer's disease subgroups. Journal of Alzheimer's disease : JAD 37: 475-481.

135. Portet F, Scarmeas N, Cosentino S, Helzner EP, Stern Y (2009) Extrapyramidal signs before and after diagnosis of incident Alzheimer disease in a prospective population study. Archives of neurology 66: 1120-1126.

136. Huang Y, Halliday G (2013) Can we clinically diagnose dementia with Lewy bodies yet? Translational neurodegeneration 2: 4.

137. Ferman TJ, Boeve BF, Smith GE, Lin SC, Silber MH, et al. (2011) Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies. Neurology 77: 875-882.

138. Chiba Y, Fujishiro H, Iseki E, Ota K, Kasanuki K, et al. (2012) Retrospective survey of prodromal symptoms in dementia with Lewy bodies: comparison with Alzheimer's disease. Dementia and geriatric cognitive disorders 33: 273-281.

139. Kraybill ML, Larson EB, Tsuang DW, Teri L, McCormick WC, et al. (2005) Cognitive differences in dementia patients with autopsy-verified AD, Lewy body pathology, or both. Neurology 64: 2069-2073.

140. Jellinger KA, Wenning GK, Seppi K (2007) Predictors of survival in dementia with lewy bodies and Parkinson dementia. Neuro-degenerative diseases 4: 428-430.

141. Kalaria RN, Ballard C (1999) Overlap between pathology of Alzheimer disease and vascular dementia. Alzheimer disease and associated disorders 13 Suppl 3: S115-123.

142. Lee JH, Olichney JM, Hansen LA, Hofstetter CR, Thal LJ (2000) Small concomitant vascular lesions do not influence rates of cognitive decline in patients with Alzheimer disease. Archives of neurology 57: 1474-1479.

143. Jellinger KA, Attems J (2006) Prevalence and impact of cerebrovascular pathology in Alzheimer's disease and parkinsonism. Acta neurologica Scandinavica 114: 38-46.

144. Esiri MM, Nagy Z, Smith MZ, Barnetson L, Smith AD (1999) Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. Lancet 354: 919-920.

145. Etiene D, Kraft J, Ganju N, Gomez-Isla T, Gemelli B, et al. (1998) Cerebrovascular Pathology Contributes to the Heterogeneity of Alzheimer's Disease. Journal of Alzheimer's disease : JAD 1: 119-134.

146. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, et al. (1997) Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA : the journal of the American Medical Association 277: 813-817.

147. Jellinger KA (2007) The enigma of mixed dementia. Alzheimer's & dementia : the journal of the Alzheimer's Association 3: 40-53.

148. Jellinger KA, Attems J (2008) Prevalence and impact of vascular and Alzheimer pathologies in Lewy body disease. Acta neuropathologica 115: 427-436.

149. Thanvi B, Lo N, Robinson T (2005) Vascular parkinsonism--an important cause of parkinsonism in older people. Age and ageing 34: 114-119.

150. Perrin RJ, Fagan AM, Holtzman DM (2009) Multimodal techniques for diagnosis and prognosis of Alzheimer's disease. Nature 461: 916-922.

151. Blennow K, Hampel H (2003) CSF markers for incipient Alzheimer's disease. Lancet neurology 2: 605-613.

152. Andreasen N, Minthon L, Davidsson P, Vanmechelen E, Vanderstichele H, et al. (2001) Evaluation of CSF-tau and CSF-Abeta42 as diagnostic markers for Alzheimer disease in clinical practice. Archives of neurology 58: 373-379.

153. Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, et al. (2006) Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet neurology 5: 228-234.

154. Zetterberg H, Hietala MA, Jonsson M, Andreasen N, Styrud E, et al. (2006) Neurochemical aftermath of amateur boxing. Archives of neurology 63: 1277-1280.

155. Hesse C, Rosengren L, Andreasen N, Davidsson P, Vanderstichele H, et al. (2001) Transient increase in total tau but not phospho-tau in human cerebrospinal fluid after acute stroke. Neuroscience letters 297: 187-190.

156. Hesse C, Rosengren L, Vanmechelen E, Vanderstichele H, Jensen C, et al. (2000) Cerebrospinal fluid markers for Alzheimer's disease evaluated after acute ischemic stroke. Journal of Alzheimer's disease : JAD 2: 199-206.

157. Riemenschneider M, Wagenpfeil S, Vanderstichele H, Otto M, Wiltfang J, et al. (2003) Phospho-tau/total tau ratio in cerebrospinal fluid discriminates Creutzfeldt-Jakob disease from other dementias. Molecular psychiatry 8: 343-347.

158. Blennow K, Johansson A, Zetterberg H (2005) Diagnostic value of 14-3-3beta immunoblot and T-tau/P-tau ratio in clinically suspected Creutzfeldt-Jakob disease. International journal of molecular medicine 16: 1147-1149.

159. Zetterberg H, Pedersen M, Lind K, Svensson M, Rolstad S, et al. (2007) Intra-individual stability of CSF biomarkers for Alzheimer's disease over two years. Journal of Alzheimer's disease : JAD 12: 255-260.

160. Blennow K, Zetterberg H, Minthon L, Lannfelt L, Strid S, et al. (2007) Longitudinal stability of CSF biomarkers in Alzheimer's disease. Neuroscience letters 419: 18-22.

161. Mattsson N, Blennow K, Zetterberg H (2009) CSF biomarkers: pinpointing Alzheimer pathogenesis. Annals of the New York Academy of Sciences 1180: 28-35.

162. Zetterberg H, Blennow K (2013) Cerebrospinal fluid biomarkers for Alzheimer's disease: more to come? Journal of Alzheimer's disease : JAD 33 Suppl 1: S361-369.

163. Wallin AK, Blennow K, Zetterberg H, Londos E, Minthon L, et al. (2010) CSF biomarkers predict a more malignant outcome in Alzheimer disease. Neurology 74: 1531-1537.

164. Bostrom F, Hansson O, Blennow K, Gerhardsson L, Lundh T, et al. (2009) Cerebrospinal fluid total tau is associated with shorter survival in dementia with Lewy bodies. Dementia and geriatric cognitive disorders 28: 314-319.

165. Lim X, Yeo JM, Green A, Pal S (2013) The diagnostic utility of cerebrospinal fluid alpha-synuclein analysis in dementia with Lewy bodies – a systematic review and meta-analysis. Parkinsonism & related disorders 19: 851-858.

166. Kasuga K, Ikeuchi T (2012) [Cerebrospinal fluid and plasma biomarkers for dementia with lewy bodies]. Brain and nerve = Shinkei kenkyu no shinpo 64: 505-513.

167. Huang CW, Chang WN, Huang SH, Lui CC, Chen NC, et al. (2013) Impact of homocysteine on cortical perfusion and cognitive decline in mild Alzheimer's dementia. European journal of neurology : the official journal of the European Federation of Neurological Societies 20: 1191-1197.

168. Jacobs D, Sano M, Marder K, Bell K, Bylsma F, et al. (1994) Age at onset of Alzheimer's disease: relation to pattern of cognitive dysfunction and rate of decline. Neurology 44: 1215-1220.

169. Ho GJ, Hansen LA, Alford MF, Foster K, Salmon DP, et al. (2002) Age at onset is associated with disease severity in Lewy body variant and Alzheimer's disease. Neuroreport 13: 1825-1828.

170. Seltzer B, Sherwin I (1983) A comparison of clinical features in early- and late-onset primary degenerative dementia. One entity or two? Archives of neurology 40: 143-146.

171. Musicco M, Palmer K, Salamone G, Lupo F, Perri R, et al. (2009) Predictors of progression of cognitive decline in Alzheimer's disease: the role of vascular and sociodemographic factors. Journal of neurology 256: 1288-1295.

172. Teri L, McCurry SM, Edland SD, Kukull WA, Larson EB (1995) Cognitive decline in Alzheimer's disease: a longitudinal investigation of risk factors for accelerated decline. The journals of gerontology Series A, Biological sciences and medical sciences 50A: M49-55.

173. Huff FJ, Growdon JH, Corkin S, Rosen TJ (1987) Age at onset and rate of progression of Alzheimer's disease. Journal of the American Geriatrics Society 35: 27-30.

174. Bracco L, Gallato R, Grigoletto F, Lippi A, Lepore V, et al. (1994) Factors affecting course and survival in Alzheimer's disease. A 9-year longitudinal study. Archives of neurology 51: 1213-1219.

175. Burns A, Jacoby R, Levy R (1991) Progression of cognitive impairment in Alzheimer's disease. Journal of the American Geriatrics Society 39: 39-45.

176. Ortof E, Crystal HA (1989) Rate of progression of Alzheimer's disease. Journal of the American Geriatrics Society 37: 511-514.

177. Stern Y, Albert S, Tang MX, Tsai WY (1999) Rate of memory decline in AD is related to education and occupation: cognitive reserve? Neurology 53: 1942-1947.

178. Rasmusson DX, Carson KA, Brookmeyer R, Kawas C, Brandt J (1996) Predicting rate of cognitive decline in probable Alzheimer's disease. Brain and cognition 31: 133-147.

179. Geerlings MI, Deeg DJ, Schmand B, Lindeboom J, Jonker C (1997) Increased risk of mortality in Alzheimer's disease patients with higher education? A replication study. Neurology 49: 798-802.

180. Wattmo C, Wallin AK, Londos E, Minthon L (2011) Long-term outcome and prediction models of activities of daily living in Alzheimer disease with cholinesterase inhibitor treatment. Alzheimer disease and associated disorders 25: 63-72.

181. Kaszniak AW, Fox J, Gandell DL, Garron DC, Huckman MS, et al. (1978) Predictors of mortality in presenile and senile dementia. Annals of neurology 3: 246-252.

182. Berg L, Danziger WL, Storandt M, Coben LA, Gado M, et al. (1984) Predictive features in mild senile dementia of the Alzheimer type. Neurology 34: 563-569.

183. Boller F, Becker JT, Holland AL, Forbes MM, Hood PC, et al. (1991) Predictors of decline in Alzheimer's disease. Cortex; a journal devoted to the study of the nervous system and behavior 27: 9-17.

184. Coen RF, Maguire C, Swanwick GR, Kirby M, Burke T, et al. (1996) Letter and category fluency in Alzheimer's disease: a prognostic indicator of progression? Dementia 7: 246-250.

185. Atchison TB, Bradshaw M, Massman PJ (2004) Investigation of profile difference between Alzheimer's disease patients declining at different rates: examination of

baseline neuropsychological data. Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists 19: 1007-1015.

186. Kraemer HC, Tinklenberg J, Yesavage JA (1994) 'How far' vs 'how fast' in Alzheimer's disease. The question revisited. Archives of neurology 51: 275-279.

187. Galasko D, Edland SD, Morris JC, Clark C, Mohs R, et al. (1995) The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part XI. Clinical milestones in patients with Alzheimer's disease followed over 3 years. Neurology 45: 1451-1455.

188. Capitani E, Cazzaniga R, Francescani A, Spinnler H (2004) Cognitive deterioration in Alzheimer's disease: is the early course predictive of the later stages? Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 25: 198-204.

189. Magierski R, Kloszewska I, Sobow TM (2010) The influence of vascular risk factors on the survival rate of patients with dementia with Lewy bodies and Alzheimer disease. Neurologia i neurochirurgia polska 44: 139-147.

190. Hanyu H, Sato T, Hirao K, Kanetaka H, Sakurai H, et al. (2009) Differences in clinical course between dementia with Lewy bodies and Alzheimer's disease. European journal of neurology : the official journal of the European Federation of Neurological Societies 16: 212-217.

191. Williams MM, Xiong C, Morris JC, Galvin JE (2006) Survival and mortality differences between dementia with Lewy bodies vs Alzheimer disease. Neurology 67: 1935-1941.

192. Olichney JM, Galasko D, Salmon DP, Hofstetter CR, Hansen LA, et al. (1998) Cognitive decline is faster in Lewy body variant than in Alzheimer's disease. Neurology 51: 351-357.

193. Lippa CF, Smith TW, Swearer JM (1994) Alzheimer's disease and Lewy body disease: a comparative clinicopathological study. Annals of neurology 35: 81-88.

194. McKeith IG, Fairbairn AF, Bothwell RA, Moore PB, Ferrier IN, et al. (1994) An evaluation of the predictive validity and inter-rater reliability of clinical diagnostic criteria for senile dementia of Lewy body type. Neurology 44: 872-877.

195. McKeith IG, Perry RH, Fairbairn AF, Jabeen S, Perry EK (1992) Operational criteria for senile dementia of Lewy body type (SDLT). Psychological medicine 22: 911-922.

196. Perry RH, Irving D, Blessed G, Fairbairn A, Perry EK (1990) Senile dementia of Lewy body type. A clinically and neuropathologically distinct form of Lewy body dementia in the elderly. Journal of the neurological sciences 95: 119-139.

197. Walker Z, Allen RL, Shergill S, Mullan E, Katona CL (2000) Three years survival in patients with a clinical diagnosis of dementia with Lewy bodies. International journal of geriatric psychiatry 15: 267-273.

198. Heyman A, Fillenbaum GG, Gearing M, Mirra SS, Welsh-Bohmer KA, et al. (1999) Comparison of Lewy body variant of Alzheimer's disease with pure Alzheimer's disease: Consortium to Establish a Registry for Alzheimer's Disease, Part XIX. Neurology 52: 1839-1844.

199. Klatka LA, Louis ED, Schiffer RB (1996) Psychiatric features in diffuse Lewy body disease: a clinicopathologic study using Alzheimer's disease and Parkinson's disease comparison groups. Neurology 47: 1148-1152.

200. Weiner MF, Risser RC, Cullum CM, Honig L, White C, 3rd, et al. (1996) Alzheimer's disease and its Lewy body variant: a clinical analysis of postmortem verified cases. The American journal of psychiatry 153: 1269-1273.

201. Ballard C, O'Brien J, Morris CM, Barber R, Swann A, et al. (2001) The progression of cognitive impairment in dementia with Lewy bodies, vascular dementia and Alzheimer's disease. International journal of geriatric psychiatry 16: 499-503.

202. Helmes E, Bowler JV, Merskey H, Munoz DG, Hachinski VC (2003) Rates of cognitive decline in Alzheimer's disease and dementia with Lewy bodies. Dementia and geriatric cognitive disorders 15: 67-71.

203. Stavitsky K, Brickman AM, Scarmeas N, Torgan RL, Tang MX, et al. (2006) The progression of cognition, psychiatric symptoms, and functional abilities in dementia with Lewy bodies and Alzheimer disease. Archives of neurology 63: 1450-1456.

204. Dumont C, Voisin T, Nourhashemi F, Andrieu S, Koning M, et al. (2005) Predictive factors for rapid loss on the mini-mental state examination in Alzheimer's disease. The journal of nutrition, health & aging 9: 163-167.

205. Wilson RS, Gilley DW, Bennett DA, Beckett LA, Evans DA (2000) Hallucinations, delusions, and cognitive decline in Alzheimer's disease. Journal of neurology, neurosurgery, and psychiatry 69: 172-177.

206. Mortimer JA, Ebbitt B, Jun SP, Finch MD (1992) Predictors of cognitive and functional progression in patients with probable Alzheimer's disease. Neurology 42: 1689-1696.

207. Scarmeas N, Brandt J, Albert M, Hadjigeorgiou G, Papadimitriou A, et al. (2005) Delusions and hallucinations are associated with worse outcome in Alzheimer disease. Archives of neurology 62: 1601-1608.

208. McKeith IG, Wesnes KA, Perry E, Ferrara R (2004) Hallucinations predict attentional improvements with rivastigmine in dementia with lewy bodies. Dementia and geriatric cognitive disorders 18: 94-100.

209. Aarsland D, Andersen K, Larsen JP, Perry R, Wentzel-Larsen T, et al. (2004) The rate of cognitive decline in Parkinson disease. Archives of neurology 61: 1906-1911.

210. Chui HC, Lyness SA, Sobel E, Schneider LS (1994) Extrapyramidal signs and psychiatric symptoms predict faster cognitive decline in Alzheimer's disease. Archives of neurology 51: 676-681.

211. Miller TP, Tinklenberg JR, Brooks JO, 3rd, Yesavage JA (1991) Cognitive decline in patients with Alzheimer disease: differences in patients with and without extrapyramidal signs. Alzheimer disease and associated disorders 5: 251-256.

212. Lopez OL, Wisnieski SR, Becker JT, Boller F, DeKosky ST (1997) Extrapyramidal signs in patients with probable Alzheimer disease. Archives of neurology 54: 969-975.

213. Scarmeas N, Albert M, Brandt J, Blacker D, Hadjigeorgiou G, et al. (2005) Motor signs predict poor outcomes in Alzheimer disease. Neurology 64: 1696-1703.

214. Larson EB, Shadlen MF, Wang L, McCormick WC, Bowen JD, et al. (2004) Survival after initial diagnosis of Alzheimer disease. Annals of internal medicine 140: 501-509.

215. Mielke MM, Rosenberg PB, Tschanz J, Cook L, Corcoran C, et al. (2007) Vascular factors predict rate of progression in Alzheimer disease. Neurology 69: 1850-1858.

216. Sanz C, Andrieu S, Sinclair A, Hanaire H, Vellas B (2009) Diabetes is associated with a slower rate of cognitive decline in Alzheimer disease. Neurology 73: 1359-1366.

217. Regan C, Katona C, Walker Z, Hooper J, Donovan J, et al. (2006) Relationship of vascular risk to the progression of Alzheimer disease. Neurology 67: 1357-1362.

218. Lee M, Chodosh J (2009) Dementia and life expectancy: what do we know? Journal of the American Medical Directors Association 10: 466-471.

219. Jagger C, Clarke M, Stone A (1995) Predictors of survival with Alzheimer's disease: a community-based study. Psychological medicine 25: 171-177.

220. Fanciulli A, Strano S, Colosimo C, Caltagirone C, Spalletta G, et al. (2013) The potential prognostic role of cardiovascular autonomic failure in alpha-synucleinopathies. European journal of neurology : the official journal of the European Federation of Neurological Societies 20: 231-235.

221. McGhee D, Counsell C (2013) Systematic review of biomarkers for disease progression in Alzheimer's disease. Journal of neurology, neurosurgery, and psychiatry 84: e2.

222. Jack CR, Jr., Shiung MM, Gunter JL, O'Brien PC, Weigand SD, et al. (2004) Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. Neurology 62: 591-600.

223. Wahlund LO, Blennow K (2003) Cerebrospinal fluid biomarkers for disease stage and intensity in cognitively impaired patients. Neuroscience letters 339: 99-102.

224. Sluimer JD, Vrenken H, Blankenstein MA, Fox NC, Scheltens P, et al. (2008) Whole-brain atrophy rate in Alzheimer disease: identifying fast progressors. Neurology 70: 1836-1841.

225. Zhang W, Arteaga J, Cashion DK, Chen G, Gangadharmath U, et al. (2012) A highly selective and specific PET tracer for imaging of tau pathologies. Journal of Alzheimer's disease : JAD 31: 601-612.

226. Craft S, Teri L, Edland SD, Kukull WA, Schellenberg G, et al. (1998) Accelerated decline in apolipoprotein E-epsilon4 homozygotes with Alzheimer's disease. Neurology 51: 149-153.

227. Martins CA, Oulhaj A, de Jager CA, Williams JH (2005) APOE alleles predict the rate of cognitive decline in Alzheimer disease: a nonlinear model. Neurology 65: 1888-1893.

228. Stern Y, Brandt J, Albert M, Jacobs DM, Liu X, et al. (1997) The absence of an apolipoprotein epsilon4 allele is associated with a more aggressive form of Alzheimer's disease. Annals of neurology 41: 615-620.

229. Hoyt BD, Massman PJ, Schatschneider C, Cooke N, Doody RS (2005) Individual growth curve analysis of APOE epsilon 4-associated cognitive decline in Alzheimer disease. Archives of neurology 62: 454-459.

230. Wattmo C, Wallin AK, Londos E, Minthon L (2011) Predictors of long-term cognitive outcome in Alzheimer's disease. Alzheimer's research & therapy 3: 23.

231. Murphy GM, Jr., Claassen JD, DeVoss JJ, Pascoe N, Taylor J, et al. (2001) Rate of cognitive decline in AD is accelerated by the interleukin-1 alpha -889 *1 allele. Neurology 56: 1595-1597.

232. Growdon JH, Locascio JJ, Corkin S, Gomez-Isla T, Hyman BT (1996) Apolipoprotein E genotype does not influence rates of cognitive decline in Alzheimer's disease. Neurology 47: 444-448.

233. Dal Forno G, Rasmusson DX, Brandt J, Carson KA, Brookmeyer R, et al. (1996) Apolipoprotein E genotype and rate of decline in probable Alzheimer's disease. Archives of neurology 53: 345-350.

234. Holmes C, Ballard C, Lehmann D, David Smith A, Beaumont H, et al. (2005) Rate of progression of cognitive decline in Alzheimer's disease: effect of butyrylcholinesterase K gene variation. Journal of neurology, neurosurgery, and psychiatry 76: 640-643.

235. Perry E, McKeith I, Ballard C (2003) Butyrylcholinesterase and progression of cognitive deficits in dementia with Lewy bodies. Neurology 60: 1852-1853.

236. Farrer LA, Cupples LA, van Duijn CM, Connor-Lacke L, Kiely DK, et al. (1995) Rate of progression of Alzheimer's disease is associated with genetic risk. Archives of neurology 52: 918-923.

237. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research 12: 189-198.

238. Wallin AK, Andreasen N, Eriksson S, Batsman S, Nasman B, et al. (2007) Donepezil in Alzheimer's disease: what to expect after 3 years of treatment in a routine clinical setting. Dementia and geriatric cognitive disorders 23: 150-160.

239. Tombaugh TN, McIntyre NJ (1992) The mini-mental state examination: a comprehensive review. Journal of the American Geriatrics Society 40: 922-935.

240. Morris JC, Edland S, Clark C, Galasko D, Koss E, et al. (1993) The consortium to establish a registry for Alzheimer's disease (CERAD). Part IV. Rates of cognitive change in the longitudinal assessment of probable Alzheimer's disease. Neurology 43: 2457-2465.

241. Clark CM, Sheppard L, Fillenbaum GG, Galasko D, Morris JC, et al. (1999) Variability in annual Mini-Mental State Examination score in patients with probable Alzheimer disease: a clinical perspective of data from the Consortium to Establish a Registry for Alzheimer's Disease. Archives of neurology 56: 857-862.

242. Doody RS, Massman P, Dunn JK (2001) A method for estimating progression rates in Alzheimer disease. Archives of neurology 58: 449-454.

243. Qaseem A, Snow V, Cross JT, Jr., Forciea MA, Hopkins R, Jr., et al. (2008) Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Annals of internal medicine 148: 370-378.

244. Palmqvist S, Minthon L, Wattmo C, Londos E, Hansson O (2010) A Quick Test of cognitive speed is sensitive in detecting early treatment response in Alzheimer's disease. Alzheimer's research & therapy 2: 29.

245. Palmqvist S, Hansson O, Minthon L, Londos E (2009) Practical suggestions on how to differentiate dementia with Lewy bodies from Alzheimer's disease with common cognitive tests. International journal of geriatric psychiatry 24: 1405-1412.

246. Mohs RC, Rosen WG, Davis KL (1983) The Alzheimer's disease assessment scale: an instrument for assessing treatment efficacy. Psychopharmacology bulletin 19: 448-450.

247. Rosen WG, Mohs RC, Davis KL (1984) A new rating scale for Alzheimer's disease. The American journal of psychiatry 141: 1356-1364.

248. Kirk A (2007) Target symptoms and outcome measures: cognition. The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques 34 Suppl 1: S42-46.

249. Stern RG, Mohs RC, Davidson M, Schmeidler J, Silverman J, et al. (1994) A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration. The American journal of psychiatry 151: 390-396.

250. Ito K, Ahadieh S, Corrigan B, French J, Fullerton T, et al. (2010) Disease progression meta-analysis model in Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 6: 39-53.

251. Fahn S ER, members of the UPDRS Development Committee. (1987) Unified Parkinson's Disease Rating Scale. In: Fahn D MC, Calne D, Goldstein M, editor. Recent development in Parkinson's disease. Florham Park, NJ: Maacmillan Healthcare Information. pp. 153-163, 293-304.

252. Ramaker C, Marinus J, Stiggelbout AM, Van Hilten BJ (2002) Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 17: 867-876.

253. El Assaad MA, Topouchian JA, Asmar RG (2003) Evaluation of two devices for self-measurement of blood pressure according to the international protocol: the Omron M5-I and the Omron 705IT. Blood pressure monitoring 8: 127-133.

254. Kaufmann H (1996) Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. Clinical autonomic research : official journal of the Clinical Autonomic Research Society 6: 125-126.

255. Gelinas I, Gauthier L, McIntyre M, Gauthier S (1999) Development of a functional measure for persons with Alzheimer's disease: the disability assessment for dementia.

The American journal of occupational therapy : official publication of the American Occupational Therapy Association 53: 471-481.

256. Schneider LS, Olin JT, Doody RS, Clark CM, Morris JC, et al. (1997) Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study. Alzheimer disease and associated disorders 11 Suppl 2: S22-32.

257. Oremus M, Perrault A, Demers L, Wolfson C (2000) Review of outcome measurement instruments in Alzheimer's disease drug trials: psychometric properties of global scales. Journal of geriatric psychiatry and neurology 13: 197-205.

258. Wolfson C, Wolfson DB, Asgharian M, M'Lan CE, Ostbye T, et al. (2001) A reevaluation of the duration of survival after the onset of dementia. The New England journal of medicine 344: 1111-1116.

259. Brodaty H, Seeher K, Gibson L (2012) Dementia time to death: a systematic literature review on survival time and years of life lost in people with dementia. International psychogeriatrics / IPA 24: 1034-1045.

260. Guehne U, Riedel-Heller S, Angermeyer MC (2005) Mortality in dementia. Neuroepidemiology 25: 153-162.

261. Brookmeyer R, Corrada MM, Curriero FC, Kawas C (2002) Survival following a diagnosis of Alzheimer disease. Archives of neurology 59: 1764-1767.

262. Boersma F, Van Den Brink W, Deeg DJ, Eefsting JA, Van Tilburg W (1999) Survival in a population-based cohort of dementia patients: predictors and causes of mortality. International journal of geriatric psychiatry 14: 748-753.

263. Koopmans RT, van der Sterren KJ, van der Steen JT (2007) The 'natural' endpoint of dementia: death from cachexia or dehydration following palliative care? International journal of geriatric psychiatry 22: 350-355.

264. Sussmuth SD, Reiber H, Tumani H (2001) Tau protein in cerebrospinal fluid (CSF): a blood-CSF barrier related evaluation in patients with various neurological diseases. Neuroscience letters 300: 95-98.

265. van der Vlies AE, Verwey NA, Bouwman FH, Blankenstein MA, Klein M, et al. (2009) CSF biomarkers in relationship to cognitive profiles in Alzheimer disease. Neurology 72: 1056-1061.

266. Kester MI, van der Vlies AE, Blankenstein MA, Pijnenburg YA, van Elk EJ, et al. (2009) CSF biomarkers predict rate of cognitive decline in Alzheimer disease. Neurology 73: 1353-1358.

267. Giordani B, Boivin MJ, Hall AL, Foster NL, Lehtinen SJ, et al. (1990) The utility and generality of Mini-Mental State Examination scores in Alzheimer's disease. Neurology 40: 1894-1896.

268. Benedict RH, Brandt J (1992) Limitation of the Mini-Mental State Examination for the detection of amnesia. Journal of geriatric psychiatry and neurology 5: 233-237.

269. Blennow K, Zetterberg H, Rinne JO, Salloway S, Wei J, et al. (2012) Effect of immunotherapy with bapineuzumab on cerebrospinal fluid biomarker levels in

patients with mild to moderate Alzheimer disease. Archives of neurology 69: 1002-1010.

270. Kraemer HC, Taylor JL, Tinklenberg JR, Yesavage JA (1998) The stages of Alzheimer's disease: a reappraisal. Dementia and geriatric cognitive disorders 9: 299-308.

271. Reisberg B, Ferris SH, de Leon MJ, Crook T (1988) Global Deterioration Scale (GDS). Psychopharmacology bulletin 24: 661-663.

272. Metzler-Baddeley C (2007) A review of cognitive impairments in dementia with Lewy bodies relative to Alzheimer's disease and Parkinson's disease with dementia. Cortex; a journal devoted to the study of the nervous system and behavior 43: 583-600.

273. Neurology TCCotAASatAAo (1996) Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. . Neurology 46: 1470.

274. Arbogast SD, Alshekhlee A, Hussain Z, McNeeley K, Chelimsky TC (2009) Hypotension unawareness in profound orthostatic hypotension. The American journal of medicine 122: 574-580.

275. Passant U, Warkentin S, Karlson S, Nilsson K, Edvinsson L, et al. (1996) Orthostatic hypotension in organic dementia: relationship between blood pressure, cortical blood flow and symptoms. Clinical autonomic research : official journal of the Clinical Autonomic Research Society 6: 29-36.

276. Schrag A, Jahanshahi M, Quinn N (2000) What contributes to quality of life in patients with Parkinson's disease? Journal of neurology, neurosurgery, and psychiatry 69: 308-312.

277. Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR (2011) The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 26: 399-406.

278. Khoo TK, Yarnall AJ, Duncan GW, Coleman S, O'Brien JT, et al. (2013) The spectrum of nonmotor symptoms in early Parkinson disease. Neurology 80: 276-281.

279. Metzler M, Duerr S, Granata R, Krismer F, Robertson D, et al. (2012) Neurogenic orthostatic hypotension: pathophysiology, evaluation, and management. Journal of neurology.

280. Burn DJ, Landau S, Hindle JV, Samuel M, Wilson KC, et al. (2012) Parkinson's disease motor subtypes and mood. Movement disorders : official journal of the Movement Disorder Society 27: 379-386.

281. Kenny RA, Kalaria R, Ballard C (2002) Neurocardiovascular instability in cognitive impairment and dementia. Annals of the New York Academy of Sciences 977: 183-195.

282. Heims HC, Critchley HD, Martin NH, Jager HR, Mathias CJ, et al. (2006) Cognitive functioning in orthostatic hypotension due to pure autonomic failure.

Clinical autonomic research : official journal of the Clinical Autonomic Research Society 16: 113-120.

283. Burn DJ, Rowan EN, Allan LM, Molloy S, O'Brien JT, et al. (2006) Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. Journal of neurology, neurosurgery, and psychiatry 77: 585-589.

284. Maule S, Milazzo V, Maule MM, Di Stefano C, Milan A, et al. (2012) Mortality and prognosis in patients with neurogenic orthostatic hypotension. Functional neurology 27: 101-106.

285. Fedorowski A, Melander O (2013) Syndromes of orthostatic intolerance: a hidden danger. Journal of internal medicine 273: 322-335.

286. Postuma RB, Gagnon JF, Pelletier A, Montplaisir J (2013) Prodromal autonomic symptoms and signs in Parkinson's disease and dementia with Lewy bodies. Movement disorders : official journal of the Movement Disorder Society 28: 597-604.

287. Chan PL, Holford NH (2001) Drug treatment effects on disease progression. Annual review of pharmacology and toxicology 41: 625-659.

288. Johansson C, Ballard C, Hansson O, Palmqvist S, Minthon L, et al. (2011) Efficacy of memantine in PDD and DLB: an extension study including washout and open-label treatment. International journal of geriatric psychiatry 26: 206-213.

289. Committee for Medicinal Products for Human Use (CHMP) (2008) Guideline on Medicinal Products for the Treatment of Alzheimer's disease and Other Dementias. London: European Medicines Agency (EMEA).

290. Camicioli R, Gauthier S (2007) Clinical trials in Parkinson's disease dementia and dementia with Lewy bodies. The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques 34 Suppl 1: S109-117.

291. Fujishiro H, Ferman TJ, Boeve BF, Smith GE, Graff-Radford NR, et al. (2008) Validation of the neuropathologic criteria of the third consortium for dementia with Lewy bodies for prospectively diagnosed cases. Journal of neuropathology and experimental neurology 67: 649-656.

292. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, et al. (1994) The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 44: 2308-2314.

293. Ferman TJ, Smith GE, Boeve BF, Ivnik RJ, Petersen RC, et al. (2004) DLB fluctuations: specific features that reliably differentiate DLB from AD and normal aging. Neurology 62: 181-187.

294. Gjerstad MD, Boeve B, Wentzel-Larsen T, Aarsland D, Larsen JP (2008) Occurrence and clinical correlates of REM sleep behaviour disorder in patients with Parkinson's disease over time. Journal of neurology, neurosurgery, and psychiatry 79: 387-391.

295. McGhee DJ, Royle PL, Thompson PA, Wright DE, Zajicek JP, et al. (2013) A systematic review of biomarkers for disease progression in Parkinson's disease. BMC neurology 13: 35.