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Markers of Prognosis in Neurodegenerative Dementia

Stubendorff, Kajsa

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Markers of Prognosis
in Neurodegenerative Dementia

Kajsa Stubendorff, MD

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DOCTORAL DISSERTATION

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Faculty Opponent

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

Primary Supervisor	**Examination Board**
Elisabet Londos, Ass. Prof	Louise Bennet, Ass. Prof.
Lund University	Lund University
Assistant Supervisor	Geir Selbaek, PhD
Lennart Minthon, Prof.	Oslo University Hospital
Lund University	Michelle Chew, Ass. Prof.
	Lund University

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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

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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

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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 neuroleptic 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 neurodegenerative dementia is DLB and PDD occurring in 15-20% and 3-4% of all dementia 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.
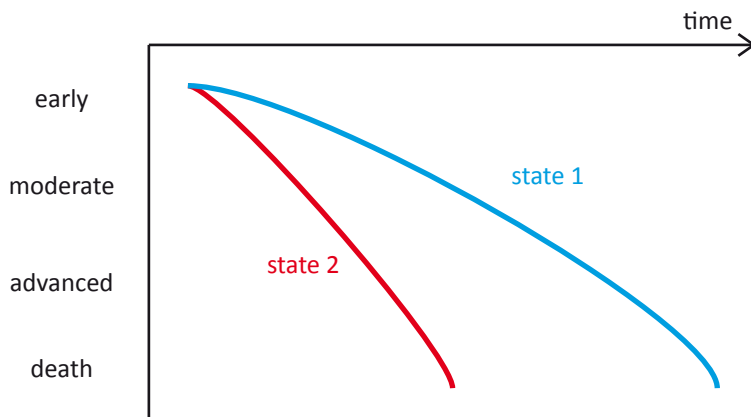
Figure 1a. A state marker is typically a diagnostic marker, responding to the question "disease yes or no". A state marker may similarly help to identify subgroups of patients within or beyond diagnostic groups.
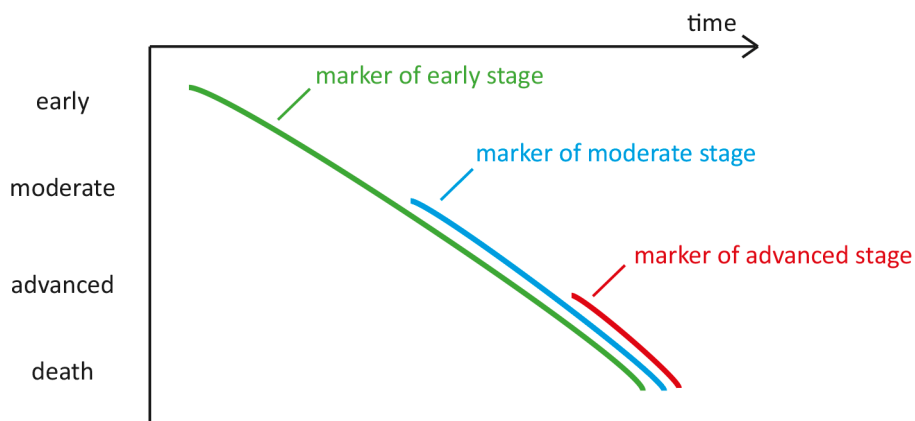
Figure 1b. Stage markers carry information on how far a patient has reached along the disease course. A stage marker indicates for example early or advanced disease stage, and can be still present as illustrated in this figure, or absent in the following (later) stages.
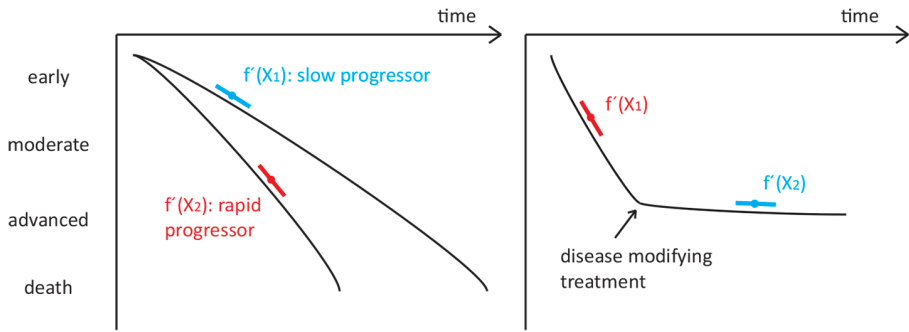
Figure 1c. Rate markers indicate the rate of progression through stages. It may tell how rapidly the disease progresses, and therefore inform prognosis. Rate markers are needed to detect true treatment effects from disease-modifying drugs, as illustrated in the right figure.

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], polypharmacy [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].
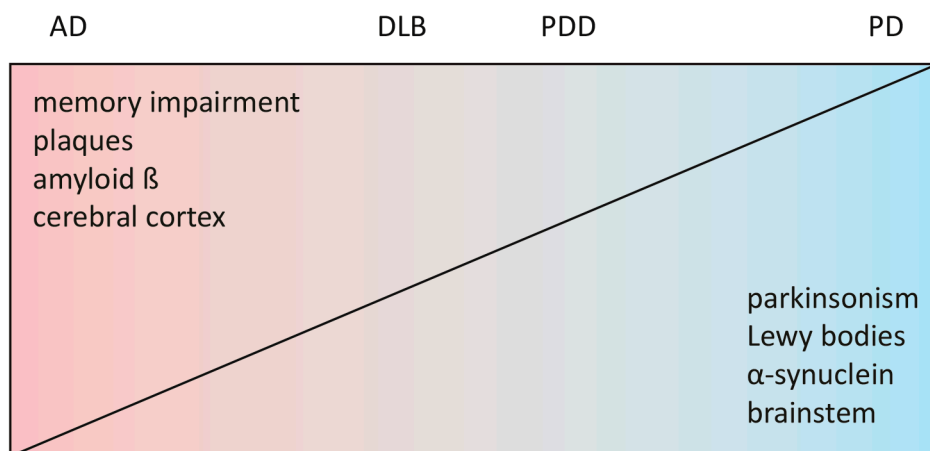
FIGURE 2: The AD-DLB/PDD-PD continuum.
Memory imparment and Parkinsonism are the cardinal symptom of AD and PD respectively. Plaques and amyloid ß are the neuropathological hallmarks of AD. Lewy bodies and α-synuclein are essential findings in PD pathology. In AD, there is a progressive atrophy of cerebral 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 *cardio-vascular 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		Retrospective	Disease onset	Mean duration of illness	No difference
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 explains 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 activity 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 dementia, 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 (χ^2) 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 (χ^2) 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 (χ^2) Mann Whitney U test Log-rank test	Survival from baseline
IV	-Treatment yes/no -Treatment response (CGIC)	Person's Chi-squared test (χ^2) 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).
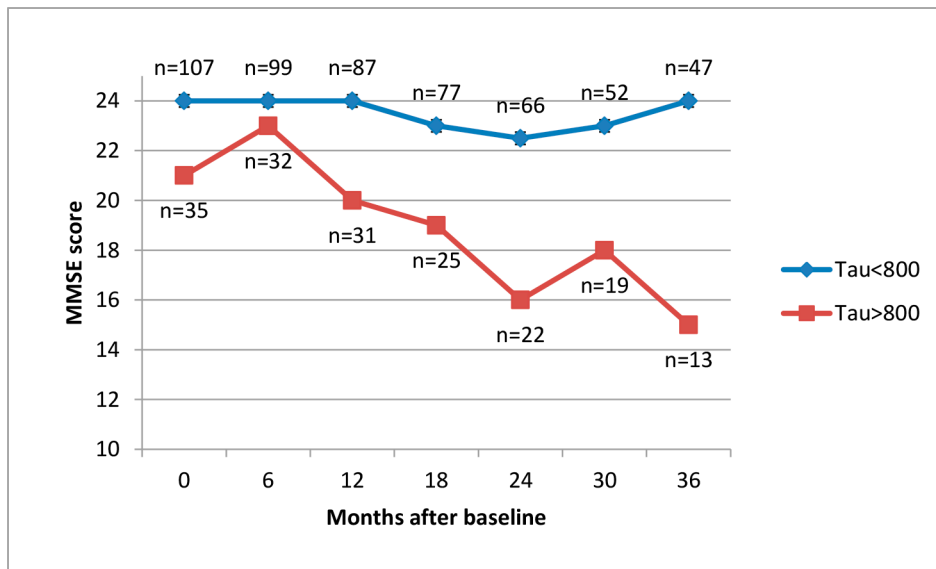

Figure 3a. MMSE scores in the two T-tau groups, during the 3-years follow-up. Every point represents the median score at baseline and at the six following visits. N=number of patients.
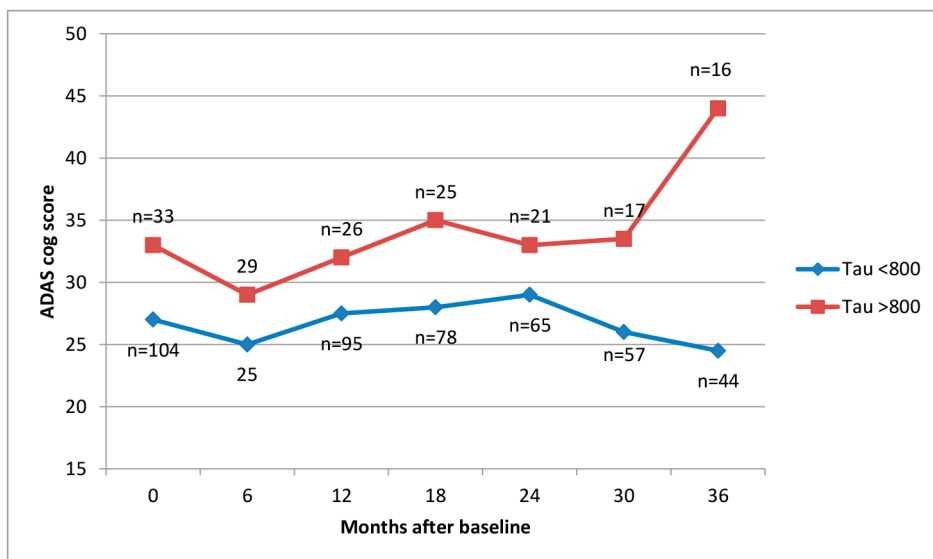
Figure 3b. ADAS-Cog scores in the two T-tau groups, during the 3-years follow-up. Every point represents the median score at baseline and at the six following visits. N=number of patients.

- 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 meaning-ful 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 sig-nificantly 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 subgroup 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 neuropsychiatric 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. High T-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.

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