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Neuropathological findings and staging in dementia

Hans Brunnström

Lund 2011

Cover image: ‘The dementia puzzle’. Histopathological features of Alzheimer’s disease (top left), vascular dementia (top right), Lewy body disease (bottom left) and frontotemporal lobar degeneration (bottom right).

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Abstract

Dementia is a clinical syndrome with the development of impairment in multiple cognitive functions (including memory), severe enough to interfere with activities of daily living, as the main symptom. There are a large number of disorders that can lead to dementia, and neuropathological examination after death is necessary to determine the underlying cause with certainty. The overall aim of this thesis was to investigate neuropathological findings in patients with dementia and neuropathological staging of dementia disorders, the main potential gain being increased epidemiological knowledge and improved neuropathological dementia diagnostics.

We could confirm the generally accepted opinion that on a neuropathological basis, Alzheimer's disease (AD) is the most common dementia disorder, followed by vascular dementia (VaD) and mixed AD+VaD. Also, in a significant number of patients, the clinical dementia subtype diagnosis does not correspond with the neuropathological findings. Furthermore, degeneration of the nucleus locus coeruleus, often seen already macroscopically, generally indicates the diagnoses Lewy body disease (LBD) or AD among the demented, while a preserved locus coeruleus occurs mainly in VaD and frontotemporal lobar degeneration (FTLD). Moreover, various neuropathological staging systems for AD differ in procedure and targeted pathology, and the choice of system affects the judgement of Alzheimer pathology and hence the final diagnosis. Also, various neuropathological LBD staging systems differ in applicability and to some extent in the judgment of Lewy-related pathology.

Keywords: Alzheimer disease, concordance, dementia, diagnostics, frontotemporal lobar degeneration, grading, Lewy body disease, locus coeruleus, neuropathology, prevalence, staging, vascular dementia

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Abbreviations

AD	Alzheimer's disease
ADDTC	State of California Alzheimer's Disease Diagnostic and Treatment Centers
CAA	Cerebral amyloid angiopathy
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CBD	Corticobasal degeneration
CDLB96	Consortium on Dementia with Lewy bodies 1996
CDLB05	Consortium on Dementia with Lewy bodies 2005
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CJD	Creutzfeldt-Jakob disease
DLB	Dementia with Lewy bodies
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, third edition, revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
FUS	Fused in sarcoma
ICD-10	International Statistical Classification of Diseases and Related Health Problems, tenth edition
IHC	Immunohistochemistry/-cal
LB	Lewy body/-ies
LBD	Lewy body disease
LC	Locus coeruleus
MCI	Mild cognitive impairment
NFT	Neurofibrillary tangle/-s

NIA-RI	National Institute on Aging–Reagan Institute
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association
NINDS-AIREN	National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences
NP	Neuritic plaque/-s
NPV	Negative predictive value
PD	Parkinson's disease
PDD	Parkinson's disease with dementia
PiD	Pick's disease
PPAD9	Poly-pathology Alzheimer's disease assessment, nine areas
PPV	Positive predictive value
PSP	Progressive supranuclear palsy
TDP-43	Transactivation-responsive DNA-binding protein 43
VaD	Vascular dementia

Original studies

This thesis is based on the following original studies, in the text referred to by their roman numbers.

I Brunnström H, Gustafson L, Passant U, Englund E. **Prevalence of dementia subtypes: a 30-year retrospective survey of neuropathological reports.** Arch Gerontol Geriatr 2009;49(1):146-149. Epub August 9, 2008.

II Brunnström H, Englund E. **Clinicopathological concordance in dementia diagnostics.** Am J Geriatr Psychiatry 2009;17(8):664-670.

III Brunnström H, Friberg N, Lindberg E, Englund E. **Differential degeneration of the locus coeruleus in dementia subtypes.** Clin Neuropathol 2011 (In press)

IV Brunnström H, Englund E. **Comparison of four neuropathological scales for Alzheimer's disease.** Clin Neuropathol 2011;30(2):56-69.

V Brunnström H, Lindberg E, Englund E. **Staging of Lewy-related pathology in dementia.** (Manuscript)

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Background

The concept of dementia

The word ‘dementia’ derives from the Latin ‘de mens’, meaning ‘without mind’. Dementia is generally defined as an acquired constellation of symptoms including impairment of memory and other cognitive functions – such as language, logic and abstract thinking – and often also changes in personality and emotion control, caused by disorders affecting the brain [Alzheimer Europe 2010a; MedlinePlus 2010]. Thus, the term ‘dementia’ does not denote one specific disease, but rather a clinical syndrome. There are several sets of dementia criteria for use in clinical practice. The two most commonly employed sets in Sweden are that of the

DSM-IV	**ICD-10**
Memory impairment (impaired ability to learn new information or to recall previously learned information). At least one of the following cognitive impairments: Aphasia (language disturbance). Apraxia (impaired ability to carry out motor activities despite intact motor function). Agnosia (impaired ability to recognise or identify objects despite intact sensory function). Executive dysfunction (planning, organising, sequencing, abstracting). The cognitive impairments above cause significant impairment in social or occupational functioning *and* represent a significant decline from a previous level of functioning. The cognitive impairments above are not only because of delirium.	Impairment of memory (registration, storage, and retrieval of new information), thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. The cognitive impairments above cause interference with personal activities of daily living *and* represent an appreciable decline in intellectual functioning. Consciousness is not clouded. The cognitive impairments above should be the effect of a disease of the brain (a condition primarily or secondarily affecting the brain). The cognitive impairments above should have been evident for at least six months.

***Table 1**. DSM-IV and ICD-10 criteria for dementia.*

Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) [American Psychiatric Association 1994] and that of the International Statistical Classification of Diseases and Related Health Problems, tenth edition (ICD-10) [World Health Organisation 1992, 2006]. The DSM-IV and ICD-10 criteria are summarised in Table 1. The two sets of criteria share a common basis: a dementia diagnosis requires the development of impairment in multiple cognitive functions including memory, and the impairment must be of such magnitude that the patient's daily life is affected. Also, the impairment must not only be present in a delirious state. There are some potentially important differences between the criteria, such as the demand for cognitive impairment for at least six months in the ICD-10 criteria. Furthermore, ICD-10 uses the term 'organic dementia', which separates substance-induced dementia from the other dementia disorders, not seen in DSM-IV.

The role of neuropathology in dementia diagnostics

As dementia is a clinical syndrome, cognitive evaluation (mainly based on anamnestic information and cognitive testing) is essential for diagnosis. However, although different dementia disorders generally have a distinct clinical presentation, neuropathological examination is necessary to differentiate between dementia subtypes with certainty. There are a great number of diseases and conditions that may cause dementia; see Table 2 for an overview (note that the relevance or even existence of some subtypes may be discussed) [based on: American Psychiatric Association 1994; Wallin *et al*. 1994; World Health Organisation 2006; Lowe *et al*. 2008; Alzheimer Europe 2010b; MedlinePlus 2009] – and there is today no alternative to neuropathology as the 'gold standard' in dementia diagnostics. Basically, a neuropathological examination is a macro- and microscopic investigation of the brain post-mortem, where different tissue staining techniques aid in the detection of histopathological findings (further described later). A brain biopsy from a living patient is, from a histological perspective, a possible alternative to the full post-mortem examination, but is not employed today as the risk and distress with such a procedure is far greater than the potential gain for the patient. The drawback with the post-mortem examination is, naturally, that the patient him- or herself can not benefit from the investigation. However, the post-mortem neuropathological examination is valuable in that it enables diagnostic feedback to the caregivers and is a basis for epidemiological knowledge, and, most of all, that it provides the patient's relatives with a certain diagnosis. Through the years, clinicopathological comparisons of demented and non-demented patients have been the basis for the identification of dementia-related pathological lesions and definitions of disease entities.

Table 2 *(opposite side). Overview of dementia subtypes (not complete).*

Major groups	Subtypes
Primary degenerative dementias	Alzheimer's disease Dementia with Lewy bodies Parkinson's disease with dementia Frontotemporal dementia (incl. corticobasal degeneration and progressive supranuclear palsy) Huntington's disease Multiple system atrophy
Vascular dementias	Large-vessel disease Small-vessel disease (incl. Binswanger's disease) Hypoperfusive-hypoxic dementia Haemorrhagic dementia Venous infarct dementia Isolated cerebral amyloid angiopathy Cerebral vasculitis: polyarteritis nodosa, temporal arteritis, systemic lupus erythematosus, etc. Hereditary vascular dementias: CADASIL, etc.
Other dementias	Brain tumour Normal-pressure hydrocephalus Head trauma Cerebral radiation Multiple sclerosis Creutzfeldt-Jakob disease Hippocampal sclerosis dementia Infections: human immunodeficiency virus, neurosyphilis, neuroborreliosis, herpes encephalitis, tuberculous meningitis, etc. Systemic metabolic disorders: hypercalcemia, hyponatremia, renal failure, hepatic failure, Wilson's disease, Hallervorden-Spatz disease, etc. Endocrine disorders: hypothyroidism, Cushing's syndrome, etc. Nutritional disorders: niacin deficiency, vitamin B12 deficiency, etc. Cerebral lipidosis: Niemann-Pick syndrome, Gaucher disease, etc. Spinocerebellar degenerations: fragile X syndrome, etc. Substance-induced dementia: alcohol, solvents, metals, pharmaceutics, etc.
Mixed dementias	(Combinations of two or more subtypes)

Notes on dementia terminology

In the field of dementia, terminology may sometimes seem a bit confusing. For the majority of the dementia disorders, the etiology and pathogenesis are not fully understood, and with progression in research new classifications and (less often) new disease entities appear every now and then. Consequently, modern terms have been invoked, while some older terms have practically ceased to be used other than in the historical perspective throughout the years. The list of dementia subtypes in Table 2 is simplified for a quick and easy overview and do not fully reflect the complex terminology used in specialised clinics and research settings, where some of the disorders are subdivided into a range of more specific entities.

The division of dementia disorders into clinical and pathological conditions further adds to the terminological complexity. For example, the term 'Alzheimer's disease' (AD) can be used for the description of both a specific clinical state and a specific pathological condition. When used as a clinical term, the diagnosis AD represents dementia (i.e., fulfilling of the dementia criteria) with gradual onset and continuing decline of cognitive functions, without any identified evidence of other systemic, substance-induced or brain disorders that could account for the cognitive deficits [McKhann *et al*. 1984; World Health Organisation 1992, 2006; American Psychiatric Association 1994]. Pathological AD, on the other hand, corresponds to the histopathological findings of a significant presence of neurofibrillary tangles (NFT), neuritic plaques (NP), neuronal cell loss et cetera [Jellinger 1998; Lowe *et al*. 2008] in a demented patient. Similar to AD, 'vascular dementia' (VaD) is also used both as a clinical and a pathological term. In contrast, it is possible to use 'dementia with Lewy bodies' (DLB) and 'Parkinson's disease with dementia' (PDD) exclusively as clinical terms, while 'Lewy body disease' (LBD) may represent the pathological findings thought to be corresponding to these clinical states (note that LBD here does not include Parkinson's disease (PD) without dementia, in contrast to the early description of diffuse LBD by Kosaka and co-workers [Kosaka *et al*. 1984]). Likewise, 'frontotemporal dementia' (FTD) may be used as a clinical term and 'frontotemporal lobar degeneration' (FTLD) as a pathological term for this group of dementia disorders. In Table 3, subtype terminology for some primary degenerative dementias is presented from both a clinical and a pathological perspective (note that the terminology, relevance or even existence of some subtypes may be discussed) [based on: Wallin *et al*. 1994; McKhann *et al*. 2001; Cairns *et al*. 2007; Lowe *et al*. 2008; Mackenzie *et al*. 2010].

In reality, there is no perfect match between the clinical and corresponding pathological conditions. Patients with the same clinical condition may exhibit

Table 3 *(opposite side). Clinical and pathological terminology for some primary degenerative dementias.*

Clinical terms/subtypes	Pathological terms/subtypes
Alzheimer's disease: Early-onset (presenile) Alzheimer's disease Late-onset (senile) Alzheimer's disease Down's syndrome with Alzheimer's disease	Alzheimer's disease: Alzheimer's disease with temporoparietal accentuation Alzheimer's disease with frontal accentuation Tangle-predominant Alzheimer's disease Plaque-predominant Alzheimer's disease Alzheimer's disease with diffuse white matter lesions
Lewy body-related dementias: Dementia with Lewy bodies Parkinson's disease with dementia	Lewy body disease
Frontotemporal dementias: Behavioural variant frontotemporal dementia Progressive non-fluent aphasia Semantic dementia Frontotemporal dementia with motor neuron disease Corticobasal degeneration Progressive supranuclear palsy	Tau-positive frontotemporal lobar degenerations: Pick's disease Corticobasal degeneration Progressive supranuclear palsy Argyrophilic grain disease Multiple system tauopathy Neurofibrillary tangle predominant dementia White matter tauopathy with globular glial inclusions Other/non-specific tau-positive frontotemporal lobar degeneration TDP-43-positive frontotemporal lobar degenerations: Frontotemporal lobar degeneration with TDP-43 inclusions Frontotemporal lobar degeneration with TDP-43 and motor neuron disease inclusions FUS-positive frontotemporal lobar degenerations: Atypical frontotemporal lobar degeneration with ubiquitin inclusions Neuronal intermediate filament inclusion disease Basophilic inclusion body disease Other frontotemporal lobar degenerations: Frontotemporal lobar degeneration with ubiquitin inclusions (TDP-43- and FUS-negative) Frontotemporal lobar degeneration with no inclusions

different histopathological features and vice versa – i.e., patients with clinical AD do not always exhibit AD pathology, while patients with AD pathology as the only histopathological finding are not always clinically classified as AD, et cetera [Galasko *et al*. 1994; Victoroff *et al*. 1995; Holmes *et al*. 1999; Jellinger 2006]. Considering this mismatch in clinical and pathological dementia phenotype, it is important to distinguish between clinical and pathological principles for the description of dementia disorders, at least until etiology and pathogenesis are better understood, as suggested in reports over a long time-span [Roth 1971; Gustafson 1996; Mathuranath *et al*. 2000]. It may be argued that AD (and other terms for dementia subtypes) should only be used as a clinicopathological term, hence restricted to patients with both a clinical picture and pathological findings in accordance with the diagnosis, something reflected in the commonly-used National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD [McKhann *et al*. 1984]. However, it does not make perfect sense not to classify a demented patient as suffering from AD, if a state of pure pathological AD (i.e., no other concomitant pathology) is found, even if the clinical condition is not best described as AD. On the other hand, important psychiatric and social aspects of mental disorders such as dementia may be missed if pathological or etiological findings are used as the sole basis for diagnosis terminology, as pointed out already by Essen-Möller [Essen-Möller 1961]. The use of one clinical diagnosis for description of the clinical state, one pathological diagnosis for the histological appearance, and one etiological-genetic diagnosis for the etiological aspect (if known) for each patient may be preferable to avoid some of the terminological confusion and to recognise all aspects of dementia as best as possible.

Dementia epidemiology

The prevalence of dementia (i.e., the proportion of individuals in a defined population having dementia at a given time) can be estimated to about 6-7% in people aged 65 years and older [based on: Jorm *et al*. 1987; Fratiglioni *et al*. 1999; Lobo *et al*. 2000; Krishnan *et al*. 2005]. Patients with impairment in one or more cognitive domains but not fulfilling the dementia criteria, classified as suffering from mild cognitive impairment (MCI) [Winblad *et al*. 2004], have been reported to represent an additional 3-19% of the senior population [Ritchie 2004]. The prevalence of dementia increases considerably with age, doubling about every five years after the age of 60-65 years, with as many as 20-40% affected in the population aged 85 years and older [Jorm *et al*. 1987; Fratiglioni *et al*. 1999; Lobo *et al*. 2000]. Considering the relatively high frequency of dementia in the elderly,

and the global increase in life expectancy over time [World Health Organisation 2009], dementia research seems to be a pressing topic.

Information on the prevalence of dementia subtypes in the population of demented patients may be useful to physicians, as it may help predict what underlying diseases to mainly suspect in patients with dementia syndrome. There are several methodological issues that affect studies on prevalence of dementia subtypes, such as the clinical dementia criteria used, if dementia subtypes were diagnosed clinically or neuropathologically, the used clinical/neuropathological diagnostic methods and criteria, interrater diagnostic variability, and selection bias of the study group.

Clinical dementia criteria: Although the widely used DSM-IV and ICD-10 classification systems [World Health Organisation 1992, 2006; American Psychiatric Association 1994] define dementia similarly (see Table 1), they are not identical, nor identical to previous versions of these classification systems or other criteria [for example: Roth *et al*. 1986]. The impact of different clinical dementia criteria on dementia prevalence has been clearly shown in studies on post-stroke patients [Pohjasvaara *et al*. 1997] and on patients with various dementia disorders [Erkinjuntti *et al*. 1997; Riedel-Heller *et al*. 2001; Pioggiosi *et al*. 2004]. For example, if the applied clinical criteria for dementia classify rather few patients with vascular lesions as demented, VaD is likely to be of lower frequency in studies on prevalence of dementia subtypes.

Dementia subtype criteria: As mentioned, there is no perfect match between clinical and pathological dementia subtype diagnoses [Galasko *et al*. 1994; Victoroff *et al*. 1995; Holmes *et al*. 1999; Jellinger 2006], and hence, prevalence of the various dementia subtypes is likely to differ if the diagnoses are based on histopathology or not. Differences in neuropathological methods and criteria (or the clinical methods and criteria, if the study is based on clinical diagnostics) for the detection and definition of different dementia subtypes may also affect the prevalence of dementia subtypes, further discussed later.

Interrater diagnostic variability: Application of criteria, whether clinical and neuropathological, may differ between individual examiners, which is why interrater variability may also affect the results of prevalence studies.

Study group selection: It is not possible to thoroughly examine the whole population of demented patients for epidemiological purposes, which is why selection bias is inevitable. The use of a randomised sample or the entire population within a limited geographic area would be preferable. This may be feasible (though not very easily) in a clinical setting, but not if the diagnoses are to be based on neuropathology. Autopsy, including neuropathological examination, is regulated by strict laws. In Sweden, an autopsy requires the initiative to refer the deceased patient to the Department of Pathology, most often by the physician who determined that all the patient's vital signs were absent. It normally also requires

the consent of the patient or, if the patient's own opinion is unknown, the consent of close relatives [Rättsnätet 1995]. Thus, pathology-based prevalence studies are very much affected by referral habits for autopsy, which is not easily controlled or corrected for. The frequency of autopsies is quite low in the whole population of demented (and also in the non-demented; the total autopsy frequency in Sweden has decreased from about 50% in the early 1970s to 14% in 2008 [Socialstyrelsen 2010]), and a relatively high rate of referral for autopsy from one department or a high rate of referral for a specific type of clinical dementia condition may cause skewing of the study population in prevalence investigations.

Epidemiology studies

There are several studies presenting neuropathological findings in unselective consecutive autopsy series or comparable more or less general dementia populations. The largest such studies found in the literature are presented in Table 4. In the table, the patients have been grouped according to the major histopathological findings (i.e., those judged significant for the dementia disorder). Thus, patients with AD and concomitant minor cerebrovascular lesions or concomitant Lewy bodies (LB) unlikely to have contributed to the dementia have been included in the AD group, while patients with AD and concomitant significant cerebrovascular lesions or concomitant significant LB burden have been included in the AD+VaD and LBD±AD groups, respectively. As seen in Table 4, AD was the most prevalent dementia subtype in all the presented studies,

Study	N	AD (%)	VaD (%)	AD+VaD (%)	LBD±AD (%)	FTLD (%)	Other (%)
Galasko *et al*. 1994	170	56.5	2.4	7.1	25.9	*	8.2
Victoroff *et al*. 1995	196	49.0	4.6	12.8	7.1	*	26.5
Jellinger 1996	540	66.3	8.5	4.1	6.1	2.8	12.2
Bowler *et al*. 1998	122	60.7	3.3	2.5	20.5	*	13.1
Akatsu *et al*. 2002	158	46.2	21.5	5.7	17.7	3.2	5.7
Barker *et al*. 2002	382	41.6	3.1	11.3	22.0	3.7	18.3
Fu *et al*. 2004	202	63.9	5.9	2.5	11.9	4.0	11.9
Jellinger 2006	1050	73.6	7.3	3.1	5.2	*	10.7

Table 4. *Prevalence of dementia subtypes in some larger studies with neuropathologically examined demented patients (with reservations due to sparse information on diagnostic considerations in some patient groups). Notes: * = FTLD included in Other dementia disorders.*

but there were also some marked differences concerning the prevalence of some subtypes. This could at least in part be explained by the methodological differences previously discussed. For example, hippocampal sclerosis was recognised as a separate dementia-causing disorder and was quite prevalent in the study by Barker and co-workers [Barker *et al*. 2002]; these patients are found among 'Other dementia disorders' in Table 4, making this group rather large. Also, in the cited studies, the authors' opinions on the boundaries between AD with minor LB burden and mixed LBD+AD are not always perfectly clear (note that both LBD and LBD+AD are considered to correspond to clinical DLB), which complicates the equivalent separation of these two groups to allow adequate comparison between the studies. Apart from this, true differences in dementia subtype prevalence may, of course, also exist due to genetic and cultural diversity.

Diagnostic concordance in dementia

Correct diagnosis is essential for the efficient treatment and care of patients, and also for the prediction of prognosis and possible complications in the course of the disease. In the field of dementia, identification of the underlying disease causing the demented state is believed to be important in this respect (motivating the use of neuropathology as the 'gold standard'). Therefore, it should be desirable to clinically identify pathological conditions correctly, preferably early in the course of the disease. Studies on agreement between clinical and pathological dementia subtype diagnoses may provide information on how reliable clinical dementia subtype diagnostics is, or rather how reliable it has been during the studied time. This may be a basis for the improvement of clinical diagnostics and criteria. There are several methodological issues that affect studies on clinicopathological concordance, such as selection bias, inclusion of non-demented control cases, the clinical diagnostic methods and criteria used, the neuropathological diagnostic methods and criteria used, interrater diagnostic variability and the statistical analysis and presentation of the data.

Study group selection: Clinicopathological studies are limited by autopsy referral habits, as previously discussed. It is plausible that patients with rare conditions and/or atypical presentation are more often referred for autopsy, which would probably decrease the diagnostic agreement rate. On the other hand, it has been argued that the autopsied dementia population may be biased towards cases with fatal dementia conditions, which could artefactually increase the diagnostic accuracy [Bowler *et al*. 1998]. The logic behind this argument may be that patients with rather aggressive dementia disorders with fatal outcomes generally have a more distinct clinical profile. Furthermore, inclusion and exclusion criteria in the clinical setup may also affect the concordance rate. The diagnostic accuracy will

be less valid in a study with narrow inclusion criteria – for example, in studies intended to investigate only one or two dementia disorders – as not only correct identification of a specific pathological state, but also correct exclusion of other pathological conditions, are of importance. The inclusion of non-demented control patients in diagnostic concordance studies most likely affects the agreement rate, as cognitively intact and MCI patients may exhibit histopathological changes in accordance with, for example, an AD diagnosis [Bennett *et al*. 2006; Price *et al*. 2009]. The inclusion of patients with normal cognition but Alzheimer pathology judged to be significant leads to a decreased clinicopathological agreement rate, but to classify such patients as suffering from AD does not make perfect sense. On the other hand, clearly non-demented young patients seldom have significant brain pathology, and to include a large group of such individuals may artefactually increase the agreement rate. It is probably best to use a broad population of demented patients, excluding non-demented individuals, in studies addressing the issue of clinicopathological diagnostic agreement.

Clinical dementia subtype diagnostics: In the clinical diagnostic work-up, there are a multitude of investigative methods and aspects that can be used or taken into account in the process of dementia subtype diagnostics. Examples of these are the patient's clinical history, symptoms and signs – including results from cognitive tests and somatic status – biochemical/laboratory tests, neuroimaging, and neurophysiological investigations. To aid in the interpretation of the findings from the investigation, clinical criteria for different dementia subtypes have been developed over the years. For AD, the criteria mainly used in more recent studies have been those of DSM-IV [American Psychiatric Association 1994], the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R) [American Psychiatric Association 1987], ICD-10 [World Health Organisation 1992, 2006], and NINCDS-ADRDA [McKhann *et al*. 1984]. For VaD, the criteria mainly employed have been those of DSM-IV [American Psychiatric Association 1994], DSM-III-R [American Psychiatric Association 1987], ICD-10 [World Health Organisation 1992, 2006], the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) [Román *et al*. 1993], the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) [Chui *et al*. 1992] and the Hachinski ischemic score [Hachinski *et al*. 1975]. The clinical criteria for DLB mainly employed have been those of the Consortium on DLB presented in 1996 (CDLB96) [McKeith *et al*. 1996] and in 2005 (CDLB05) [McKeith *et al*. 2005], while criteria for FTD have been defined by the Lund and Manchester groups, Neary and co-workers and McKhann and co-workers, respectively [Lund and Manchester Groups 1994; Neary *et al*. 1998; McKhann *et al*. 2001]. The criteria for each dementia subtype are not identical, and the impact of this fact has been shown for AD and VaD in several investigations [Wetterling *et al*. 1996; Jobst *et al*. 1998; Pohjasvaara *et al*. 2000; Gold *et al*. 2002; Knopman *et al*. 2003a; Rasquin *et al*. 2005; Bacchetta *et al*.

2007]. Consequently, which clinical dementia subtype criteria that are used, affect the results of studies on clinicopathological diagnostic concordance.

Neuropathological dementia subtype diagnostics: The multitude of clinical criteria has its equivalence in the neuropathological setting. For example, some commonly employed neuropathological AD criteria have been those by Khachaturian (reporting for the National Institute on Aging) [Khachaturian 1985], the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [Mirra *et al*. 1991], Braak and Braak (hereafter referred to as Braak) [Braak & Braak 1991], and by the National Institute on Aging–Reagan Institute (NIA-RI) [National Institute on Aging, and Reagan Institute Working Group 1997]. None of these criteria are identical, which has been addressed in some investigations [Geddes *et al*. 1997; Nagy *et al*. 1998a; Newell *et al*. 1999].

Interrater diagnostic variability: Application of criteria, whether clinical or neuropathological, may differ between individual examiners, why interrater variability may also affect the results of concordance studies [Baldereschi *et al*. 1994; Lopez *et al*. 1999; Hogervorst *et al*. 2000]. Neuropathological diagnostics and interrater variability are further discussed later.

Data presentation: Statistical analysis and presentation of data can also affect the clinicopathological diagnostic concordance, or rather how the concordance is interpreted and understood. A common way to present diagnostic concordance data in fields where a 'gold standard' exists is in the form of values for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Sensitivity is defined as the proportion of actual positives which are correctly identified as such, e.g., the percentage of patients with pathological AD who are clinically identified as having the condition. Specificity is defined as the proportion of actual negatives which are correctly identified, e.g., the percentage of patients without pathological AD who are not clinically diagnosed as AD. PPV is the proportion of individuals with a positive test result who are correctly diagnosed, e.g., the percentage of patients with a clinical AD diagnosis who have pathological AD. NPV is the proportion of patients with a negative test result who are correctly diagnosed, e.g., the percentage of patients with a clinical diagnosis other than AD that do not have pathological AD. In Table 5, the mathematical formulas for calculating sensitivity, specificity, PPV and NPV are presented. It may be concluded that in order to achieve a valid value for sensitivity for AD, an unselective population of cases with neuropathological AD is required, while the calculation of PPV for AD requires an unselective population of cases with clinical AD. On the other hand, the calculation of specificity and NPV requires a broad population of demented patients, preferably as similar to the general population of demented patients as possible. Any selection bias in the study population will most of all have an effect on specificity and NPV. There are at least two problems relating to this issue. Firstly, clinicopathological studies

	Pathological criteria fulfilled	Pathological criteria not fulfilled
Clinical criteria fulfilled	a	b
Clinical criteria not fulfilled	c	d
Sensitivity = a/(a+c) Specificity = d/(b+d) Positive predictive value = a/(a+b) Negative predictive value = d/(c+d)		

***Table 5**. Mathematical formula for sensitivity, specificity and predictive values.*

depend on referral habits for autopsy, as previously discussed, meaning that there will be a risk of selection bias. Secondly, mixed pathology is common in demented patients [Petrovitch *et al*. 2005; Kovacs *et al*. 2008; Jellinger 2009], which complicates the calculation of sensitivity, specificity and predictive values. Patients are often clinically diagnosed a rather long time before death and are not always followed-up regularly during their last years. Additional pathology may appear late in the course, after the clinical diagnostic work-up, but is still regarded at the neuropathological examination. For example, sensitivity for AD can be calculated as the proportion of the patients with pathologically pure AD who were clinically diagnosed as suffering from AD. If so, specificity is calculated as the proportion of patients without pathologically pure AD – but including patients with pathological AD in combination with other pathology – who were clinically diagnosed as not suffering from AD. In this case, a patient with clinical AD and pathological AD+VaD will decrease the specificity, which does not make perfect sense, considering the discrepancy in time between the clinical and pathological examination. It would probably be more accurate to define specificity as the proportion of patients with a clinical diagnosis other than AD that did not have AD pathologically, either alone or with other pathology. However, in this case, sensitivity will be unjustly low, as a patient diagnosed both clinically and pathologically as AD+VaD will decrease the sensitivity for AD, which does not make perfect sense either. Hence, sensitivity and specificity may not be the best way to describe clinicopathological concordance in dementia diagnostics.

Another way to present diagnostic concordance is to calculate percent agreement, i.e., the percentage of patients in the whole study population that were identically diagnosed clinically and pathologically. Here, it is possible to take mixed dementias into account, as the proportion of patients with a clinical diagnosis partially in agreement with the pathological findings may be presented separately.

However, percentage agreement is not chance-corrected. If the clinical and pathological diagnoses, respectively, were randomly distributed among the studied patients, there would be some clinicopathological concordance by chance. This can be corrected for by using the kappa value instead of simple percent agreement [see: Altman 1991]. Although the kappa value seems to be more adequate, it does not take mixed pathology and partial agreement into account. Weighted kappa can be used to achieve this in ordinal or continuous data, but not in nominal data (essentially, the problem is that it is impossible to determine which is more incorrect, a clinical diagnosis of FTD or of VaD in a patient with pathological AD – something required for weighted kappa). It is plausible that the presentation of sensitivity/specificity, percent agreement or kappa value can affect how the results from clinicopathological diagnostics concordance studies are interpreted, especially if the meaning of the terms is not perfectly clear to the reader.

Concordance studies

There are several studies in the literature presenting data on clinicopathological concordance in dementia diagnostics. The largest such studies found of those that have used a broad population of demented patients and have been published since the mid 1990s are presented in Table 6 and Table 7. There are many more concordance studies with a rather limited number of included patients and/or a more selective study population from the same period of time [for example: Gearing *et al.* 1995; Klatka *et al.* 1996; Rasmusson *et al*. 1996; Gold *et al*. 1997; Berg *et al*. 1998; Litvan *et al*. 1998; Lopez *et al*. 1999; Nagy *et al*. 1998b; Luis *et al*. 1999; Verghese *et al*. 1999; Hohl *et al*. 2000; McKeith *et al*. 2000; Gold *et al*. 2002; Bacchetta *et al*. 2007; Fujishiro *et al*. 2008; Gay *et al*. 2008]. In Table 6, the concordance for AD is presented, while Table 7 addresses VaD. In addition to population size (excluding any non-demented control subjects when possible) and the employed clinical and pathological criteria for the dementia subtype, the tables show sensitivity, specificity and predictive values collected or calculated from the data in the cited articles. The results are for clinical AD or VaD (both 'probable' and 'possible' in case of NINCDS-ADRDA [McKhann *et al*. 1984] or NINDS-AIREN criteria [Román *et al*. 1993], but not mixes such as AD+VaD) to detect pathological AD or VaD, respectively, alone or in combination with other pathology. If 'probable' clinical AD or VaD, respectively, were to be analysed separately – with 'possible' cases grouped together with other dementia diagnoses – or if only the pure pathological forms and unmixed cases were to be detected, the figures would be different from those presented.

As seen in Table 6, sensitivity and PPV are generally quite high for AD, while specificity and NPV are rather limited. In the clinical setting, this means that a patient with a clinical AD diagnosis is likely to have significant AD pathology, but

Study	N	Clinical criteria	Pathological criteria	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
Galasko *et al*. 1994	170	NINCDS-ADRDA	Khachaturian	84	42	90	30
Victoroff *et al*. 1995	196	NINCDS-ADRDA	CERAD *or* Khachaturian	81	59	86	48
Bowler *et al*. 1998	122	NINCDS-ADRDA *and* DSM-III-R #	CERAD	85	45	82	50
Jobst *et al*. 1998	104	NINCDS-ADRDA *and* DSM-III-R	CERAD	96	38-46	84-86	75-79
Holmes *et al*. 1999	80	NINCDS-ADRDA	CERAD	79	30	89	17
Lim *et al*. 1999	123	NINCDS-ADRDA	CERAD	90	41	80	61
Massoud *et al*. 1999	89 *	NINCDS-ADRDA	CERAD *or* Khachaturian	96	82	90	93
Hogervorst *et al*. 2003	204 *	NINCDS-ADRDA	CERAD	86	46	70	69
Jellinger 2006	1050	NINCDS-ADRDA *and* DSM-IV #	Braak *and* CERAD *and* NIA-RI #	68	69	93	26
Plassman *et al*. 2006	175	NINCDS-ADRDA	CERAD *or* NIA-RI	85	31	86	29
Ranginwala *et al*. 2008	313 *	NINCDS-ADRDA ¤	Braak *and* CERAD *and* NIA-RI #	85	64	86	61

Table 6. *Studies on clinicopathological concordance in AD diagnostics with broad populations of demented (with reservations due to sparse information on diagnostic considerations in some patient groups). Notes:* ******* *= including some non-demented individuals; # = unclear which criteria used if not in accordance with each other; ¤ = all types of clinical AD (e.g., including mixed AD+VaD).*

a clinical diagnosis other than AD does not necessarily rule out the presence of significant AD pathology. For VaD, the sensitivity is rather low, while the other parameters are relatively high in the studies cited in Table 7. However, the number

Study	N	Clinical criteria	Pathological criteria	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
Galasko *et al*. 1994	170	DSM-III-R	N/A	25	99	80	93
Victoroff *et al*. 1995	196	N/A	N/A	15	96	45	84
Bowler *et al*. 1998	122	N/A	N/A	29	100	100	96
Holmes *et al*. 1999	80	NINDS-AIREN	N/A	44	96	83	81
Massoud *et al*. 1999	89 *	NINDS-AIREN	N/A	4	100	100	70
Knopman *et al*. 2003a	89	ADDTC *and* NINDS-AIREN *and* ICD-10 *and* DSM-IV *and* Knopman et al., 2002	N/A	22-74	70-98	46-83	78-88
Jellinger 2006	1050	N/A	N/A #	65	96	68	96

***Table** 7. Studies on clinicopathological concordance in VaD diagnostics with broad populations of demented (with reservations due to sparse information on diagnostic considerations in some patient groups). Notes: * = including some non-demented individuals; # = refers to criteria-like description [Jellinger, 2005].*

of patients with a clinical diagnosis of VaD is quite small, with no more than a dozen cases in most studies, which makes the figures uncertain. In the literature, there is only a single study with a broad population of demented patients primarily addressing the issue of clinicopathological concordance in DLB [Verghese *et al*. 1999]. However, it includes a rather limited number of patients (n = 62), which is also true for other studies on the same issue with more selective study populations [Litvan *et al*. 1998; Luis *et al*. 1999; Hohl *et al*. 2000; McKeith *et al*. 2000]. Still, these studies indicate that the diagnostic agreement is fairly good, with a PPV in the range of about 50-95%. Broad studies with a reasonable number of patients with FTD for evaluation of the concordance of this family of diseases have not yet been presented.

Neuropathological dementia diagnostics

As previously mentioned, a neuropathological examination connotes a macro- and microscopic investigation of the brain. The brain is fixed in diluted formalin, usually for a few weeks, before being sectioned and further examined. Normally, the cerebrum and diencephalon are cut in coronal slices, and the brainstem and cerebellum in horizontal slices, under macroscopic inspection. Several regions of the brain are then selected for microscopic evaluation, and the tissue is dehydrated and embedded in paraffin before sectioning. The histological sections, normally 4-7 μm thick, are stained with various tissue staining techniques to detect specific histopathological features. The employment of a standard procedure for the selection of stains and brain areas to examine microscopically may be advantageous as it engenders a systematic approach to histopathological evaluation. The standard in Lund is presented in Study II. However, the exact neuropathological procedure varies between diagnostic centres. Also, the selection of stains and brain areas for examination is often guided by the clinical information and macroscopic findings in the individual case, as a comprehensive investigation is not always possible in daily practice.

Histopathological stains

Histopathological stains are divided into conventional and immunohistochemical (IHC) stains. Conventional stains include chemical dyes and metal-based impregnations, and basically create contrast by differences in affinity for the various elements of the tissue. IHC stains are based on the binding of antibodies to a specific epitope (typically protein structures), thus identifying one specific structure in the tissue. The IHC stains are generally more sensitive and sometimes more easily manageable than the conventional ones, and have to a large extent replaced the latter in dementia diagnostics in many pathology departments. However, IHC stains are used only on small tissue cassettes, while conventional stains can be used on large areas such as whole coronal sections, if the appropriate equipment and trained technicians exist.

The conventional stains most frequently used in dementia diagnostics are haematoxylin-eosin, luxol fast blue, alkaline Congo red and different silver stains such as Gallyas, Campbell and modified Bielschowsky (the latter practically no longer in use due to high silver consumption). Haematoxylin-eosin is the universal standard stain in the field of histopathological diagnostics. Basically, the haematoxylin component stains basophilic structures such as cell nuclei deeply blue, while the eosin stains acidophilic structures such as cytoplasm and extracellular matrix in various shades of pink. Luxol fast blue stains myelin blue, and is useful for the examination of white matter. Congo red stains amyloid

deposits, such as the cores of NP and amyloid in the walls of the small meningocortical vessels (called cerebral amyloid angiopathy; CAA). With this stain, the amyloid is red in a normal light microscope, and light green if a polarised filter is used. Silver stains are mainly used for the detection of NFT and NP – the hallmarks of AD – but some may also visualise CAA and tau-positive FTLD inclusions. The different silver stains vary in their sensitivity for NFT and plaques [Rosenwald *et al*. 1993; Uchihara 2007]. The Gallyas stain is sensitive for NFT, but is not the most sensitive silver stain for plaques (e.g., it labels NP but not diffuse plaques). The Campbell silver stain, on the other hand, is more sensitive for plaques, but much less so for NFT.

The IHC stains most frequently used in dementia diagnostics are those for the proteins tau, β-amyloid, α-synuclein, ubiquitin and transactivation-responsive DNA-binding protein 43 (TDP-43). Other less frequently employed IHC stains are those for the fused in sarcoma (FUS) protein, neurofilament protein, prion protein, glial fibrillary acidic protein and others. The discovery that most neurodegenerative diseases exhibit intracellular accumulation of abnormally configured proteins, in modern neuropathology primarily visualised with IHC stains, has led to the concept of 'proteinopathies', with the grouping of diseases according to the type of protein accumulations, e.g., 'tauopathies', 'synucleinopathies', 'TDP-43 proteinopathies' and 'FUS proteinopathies'. Pathological accumulation of tau protein is found in NFT, NP and in intracellular inclusions in some types of FTLD, including Pick's disease (PiD), corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP). The β-amyloid peptide is found in NP cores and in small vessel walls of CAA. The α-synuclein protein is found in LB and Lewy neurites – the hallmarks of PD and LBD – and also in intracellular glial cell inclusions in multiple system atrophy. The ubiquitin protein is a protein degradation marker, which accumulates in several pathological structures such as NFT, NP, LB, and intracellular inclusions in almost all types of tau-negative FTLD and also in amyotrophic lateral sclerosis (today, the ubiquitin stain is often replaced by the p62 IHC stain). In the very majority of cases, the recently described TDP-43 protein [Neumann *et al*. 2006] is found in the ubiquitin/p62-positive intracellular inclusions in tau-negative FTLD and amyotrophic lateral sclerosis. The recently described FUS [Neumann *et al*. 2009] and neurofilament protein IHC stains are also used in the subtype diagnostics of FTLD. The stains for prion and glial fibrillary acidic protein are used for the detection of Creutzfeldt-Jakob disease (CJD) and for the assessment of an increase in the number of glial cells (gliosis), respectively. [Dickson 2005; Lowe *et al*. 2008; Kovacs & Budka 2010]

The neuropathology of Alzheimer's disease

Macroscopic features: In AD, the typical macroscopic findings are symmetric

cortical atrophy and ventricle widening, and depigmentation of the noradrenaline-producing pontine nucleus locus coeruleus (LC). The cortical atrophy may be seen as narrowing of gyri and widening of sulci, especially in the temporal, parietal and frontal lobes, but does not necessarily have to be very prominent. The lateral and the third ventricles are commonly enlarged, as well as the Sylvian fissure, usually reflecting the degree of cortical atrophy (this secondary widening of the ventricles is seen in practically all diseases affecting the cerebral cortex and/or white matter). The medial temporal lobe, containing the hippocampus and entorhinal cortex, is typically involved early in the disease. The amygdala may also be atrophied, and depigmentation of the dopamine-producing mesencephalic nucleus substantia nigra is sometimes seen. [Lowe *et al*. 2008]

Microscopic features: In the microscope, patients with AD by definition present with NFT and NP. NFT are intraneuronal flame-shaped or globose structures, while NP are larger extracellular round structures with a central β-amyloid core surrounded by dystrophic neurites. NFT, neuropil threads – threadlike tau-positive structures – and dystrophic neurites are classified as neurofibrillary changes. Amorphous plaques without an amyloid core (and usually without dystrophic neurites), called diffuse plaques, are also found in addition to NP. Furthermore, AD cases invariably exhibit cortical neuronal shrinkage and loss, and gliosis (astrocytic and microglial). Micro-vacuolisation in the cerebral cortex is often seen as a result of neuronal loss, but may be obscured in severe degeneration with cortical atrophy and collapse. With increasing degeneration, the normal cytoarchitectural order vanishes. Moreover, a decrease in the number of synapses may be detected with appropriate IHC staining. In cases with mild AD, pathological lesions are typically restricted to the medial temporal lobe including the hippocampus, with spread to the temporal, the parietal, and eventually the occipital and frontal lobes in severe cases. [Brun & Englund 1981; Braak & Braak 1991; Jellinger & Bancer 1998; Lowe *et al*. 2008] A significant presence of CAA is common but not mandatory in AD. Also, more than half of AD cases exhibit diffuse/non-focal white matter lesions (in the absence of vascular pathology), with the loss of myelin-stained fibres not proportional to the expected level due to cortical neuronal degeneration [Brun & Englund 1986; Englund 1998]. These white matter lesions, sometimes called selective incomplete white matter infarctions, may be regarded as a complication to the neurodegenerative disease, and have been linked to, but not fully explained by, the presence of CAA [Haglund *et al*. 2002]. Degeneration of the LC, often also seen macroscopically, and of the nucleus basalis, is common in AD. Degeneration of the substantia nigra is less frequent, but may occur [Lyness *et al*. 2003]. Images of some common neuropathological findings in AD are seen in Figure 1.

Molecular aspects: On the molecular level, the tau and β-amyloid proteins are central in AD. The normal tau protein plays a role in stabilising microtubules in the neuronal axon. The tau protein is hyperphosporylated in its pathological form,

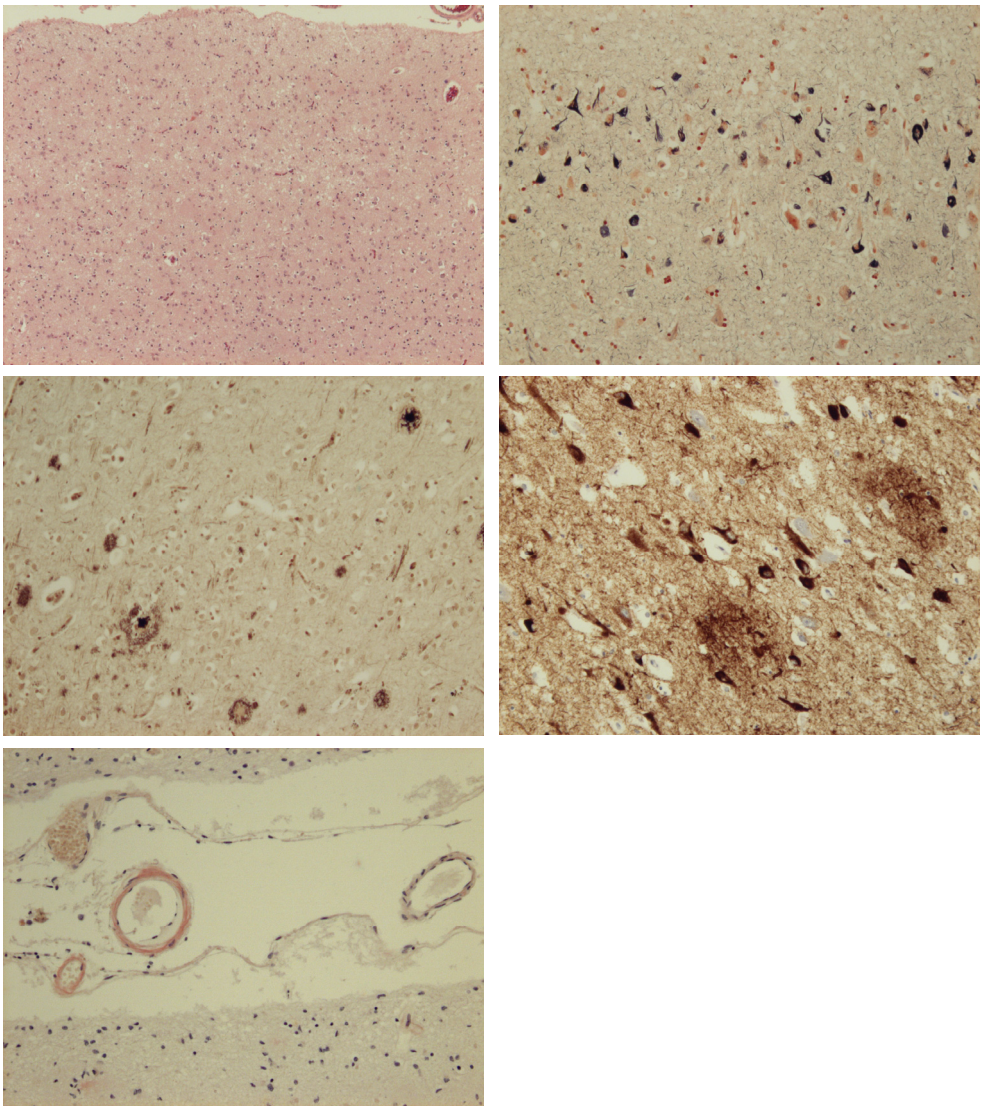

***Figure 1**. Common histopathological findings in Alzheimer's disease. Cortical degeneration with loss of neurons, micro-vacuolisation, cytoarchitectural disorder and gliosis. Haematoxylin-eosin staining, x4 objective (**upper left**). Neurofibrillary tangles and neuropil threads. Gallyas silver staining, x10 objective (**upper right**). Neuritic plaques with/without dense amyloid core. Campbell silver staining, x10 objective (**middle left**). Neurofibrillary tangles, neuropil threads and plaques. Immunohistochemical staining for tau, x10 objective (**middle right**). Cerebral amyloid angiopathy in leptomeningial vessels (red vessel walls). Alkaline Congo red staining, x10 objective (**lower left**). For white matter disease, see Figure 2.*

leading to protein aggregation and subsequent formation of paired helical filaments, the main constituents of neurofibrillary pathology. The tau protein exists in several isoforms, and accumulation of different (or partly different) isoforms is seen in AD and the various tau-positive FTLD subtypes. The β-amyloid peptide, which accumulates in NP and CAA, is a misfolded product of proteolytic cleavage of the transmembranous amyloid precursor protein, a protein possibly involved in neuronal cell growth and plasticity. There are several known mutations in the amyloid gene and in associated genes that inevitably lead to AD, often at quite a young age. In contrast, mutation in the tau gene is linked to FTLD, not AD, which supports the hypothesis that the β-amyloid peptide is at the start of the pathological pathway leading to AD. [Buée *et al*. 2000; Heese & Akatsu 2006; Lowe *et al*. 2008]

Neuropathological criteria: Several different sets of neuropathological criteria (or criteria-like assessment descriptions) for AD have been presented over the years. In addition to the previously mentioned Khachaturian [Khachaturian 1985], CERAD [Mirra *et al*. 1991], Braak [Braak & Braak 1991; Braak *et al*. 2006a], and NIA-RI [National Institute on Aging, and Reagan Institute Working Group 1997], there are also the criteria by Tierney and co-workers [Tierney *et al*. 1988], Jellinger and Bancher [Jellinger & Bancer 1997], Snowdon and co-workers (the Nun study) [Snowdon *et al*. 1997] and McKeel and co-workers (the Washington University criteria) [McKeel *et al*. 2004]. In all the cited criteria, AD diagnosis is based on the extent of tangles and/or plaques, some also taking patient age or cognitive status into account. In Lund, the assessment of Alzheimer pathology has been based on neuronal loss, micro-vacuolisation, gliosis, cytoarchitectural disorder and cortical atrophy, in addition to the presence of tangles and plaques [Brun & Englund 1981].

The neuropathology of vascular dementia

VaD is a heterogeneous entity in that several types of vascular lesions may lead to dementia. VaD is commonly separated into the groups large-vessel disease, small-vessel disease, hypoperfusive-hypoxic dementia, and the less frequent forms venous infarct dementia, haemorrhagic dementia and dementia due to isolated CAA, cerebral vasculitis and hereditary diseases such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (see Table 2). In reality, a mix of two or more types of vascular lesions is common in patients with VaD.

Pathological features: Large-vessel lesions include large territorial and strategically located arterial infarcts, and are typically due to arteriosclerosis with subsequent thrombosis or embolism. VaD caused by several large territorial infarcts is often referred to as multi-infarct dementia. Infarcts in anatomical locations such as the thalamus, basal forebrain and hippocampus lead to cognitive

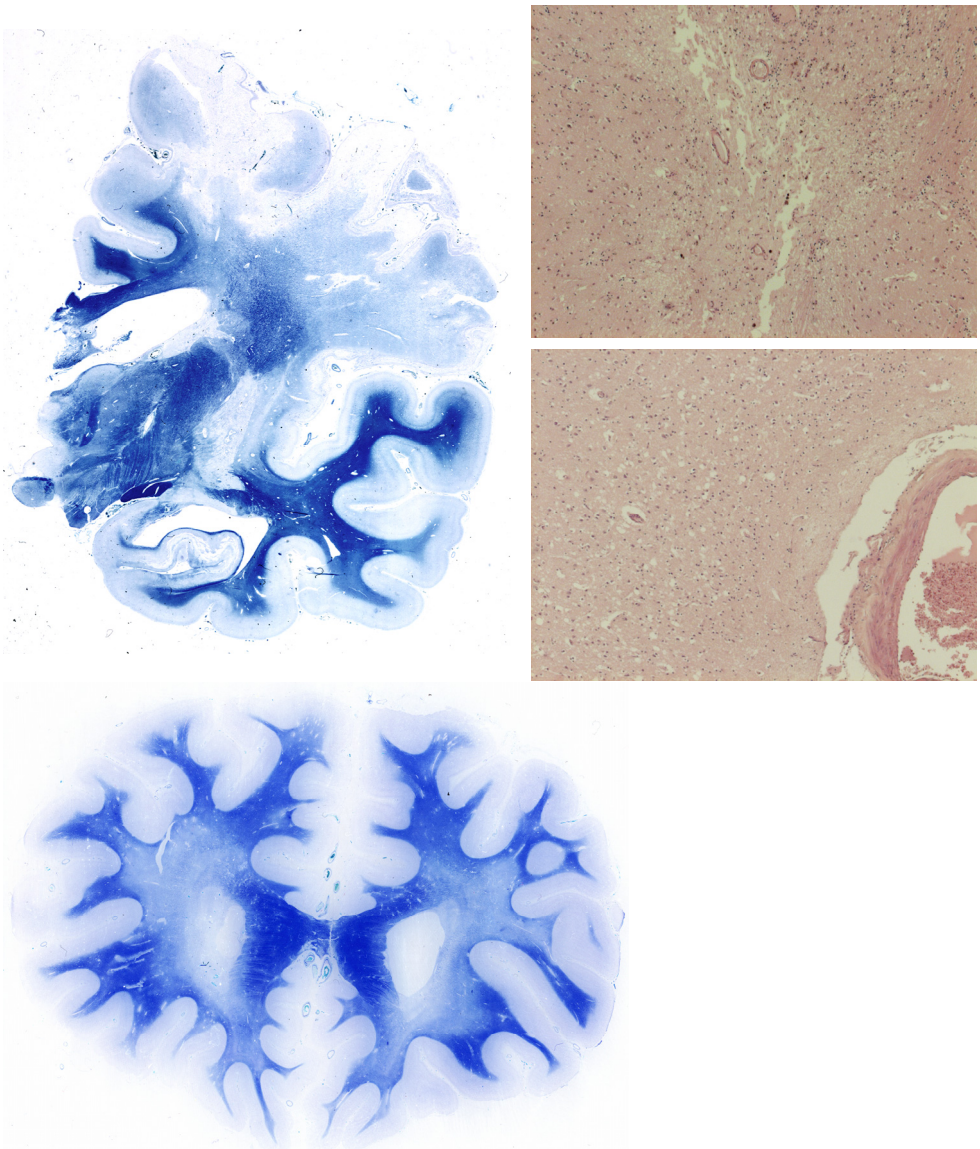

***Figure 2**. Common histopathological findings in vascular dementia. Large arterial infarction. Luxol fast blue staining, coronal hemispheric section at the level of anterior hippocampus (**upper left**). Subcortical microinfarct. Haematoxylin-eosin staining, x4 objective (**upper right**). Hypoxic-hypoperfusive cortical degeneration with micro-vacuolisation, and arteriosclerotic blood vessel. Haematoxylin-eosin staining, x4 objective (**middle right**). Periventricular white matter disease. Luxol fast blue staining, coronal whole brain section of the frontal lobes (**lower left**).*

impairment disproportionate to the size of the infarct, and are therefore called strategic. Small-vessel lesions include lacunar infarcts (small subcortical infarcts), cortical micro-infarcts and ischemic white matter lesions. Small-vessel lesions are typically seen in patients with hypertension and arteriolosclerosis. Hypoperfusive-hypoxic lesions include border zone infarcts (infarcts in areas where artery supply territories border), cortical laminar necrosis, ischemic cortical degeneration, ischemic white matter lesions and ischemic hippocampal sclerosis. The diffuse, or non-infarct, ischemic lesions are particularly difficult to diagnose, and may be seen only at post-mortem neuropathological examination. Isolated CAA (in the absence of AD) may be hereditary or sporadic, and typically leads to cerebral haemorrhages, ischemic white matter lesions and small infarcts. Intracranial haemorrhages are often caused by hypertension, treatment with anticoagulants, trauma or tumours, in addition to CAA. [Román *et al*. 1993; Brun 1994; Kalaria *et al*. 2004; Ferrer *et al*. 2008; Lowe *et al*. 2008] Images of some common neuropathological findings in VaD are seen in Figure 2.

Neuropathological criteria: In the literature, there are some different criteria for VaD, such as the NINDS-AIREN [Román *et al*. 1993], the ADDTC (ischemic VaD) [Chui *et al*. 1992] and the criteria proposed by Erkinjuntti (subcortical VaD) [Erkinjuntti 2002]. However, from a neuropathological perspective, these criteria are only categorisations of vascular lesions, as no specific quantitative requirements of lesions are presented, also seen in other reports addressing the issue [Brun 1994; Kalaria *et al*. 2004; Jellinger 2005]. On the whole, the basis for VaD diagnosis is simply the presence of brain lesions related to vascular pathology. In some reports the exclusion of other types of dementia-related pathology is required for diagnosis [Román *et al*. 1993; Kalaria *et al*. 2004]. The lack of actual criteria may be seen as proof of VaD being difficult to define or quantify neuropathologically, and consequently, a VaD diagnosis very much depends on the neuropathologist's judgement.

The neuropathology of Lewy body disease

Macroscopic features: In LBD, here used as a term for the pathological substrate for clinical PDD and DLB, a macroscopic depigmentation of the LC and the substantia nigra is practically always seen. LBD cases may also exhibit mild cortical atrophy, mainly apparent in the frontal lobes, and sometimes there is atrophy of the temporal lobe, especially in cases with concomitant Alzheimer pathology. Apart from this, there are generally no macroscopic pathological findings in LBD cases. [Lowe *et al*. 2008]

Microscopic features: In the microscope, patients with LBD by definition present with widespread LB. LB are α-synuclein-containing intraneuronal inclusions, spherical with a dense core and a clear halo in the brainstem, oval or irregular in the cortex. In LBD, α-synuclein-positive Lewy neurites are also seen in the

cerebral cortex, and pale bodies – regarded as pre-stages of LB – may be seen in the brainstem, the two classified as Lewy-related pathology together with LB. In mild disease, Lewy-related pathology affects the brainstem, with spread to limbic structures and the neocortex in more severe cases. In addition to Lewy-related pathology, concomitant Alzheimer pathology, especially in the form of diffuse plaques, but also NFT and NP, is common in LBD. Furthermore, neuronal loss is often seen in LBD, but without the prominent neurodegeneration with atrophy seen in AD. CAA may also be seen. The clinical diagnoses PDD and DLB are separated based on the debut of cognitive symptoms in relation to parkinsonism (DLB requires cognitive symptoms before or starting within a year after the onset of parkinsonism). Pathologically, concomitant Alzheimer pathology is seen more often in DLB than in PDD, but on the whole, the DLB/PDD separation may not be of importance from a neuropathological perspective. [McKeith *et al*. 2005; Ince *et al*. 2008; Jellinger & Attems 2008a; Lowe *et al*. 2008] Images of some common neuropathological findings in LBD are seen in Figure 3.

Neuropathological criteria: The first consensus criteria for LBD were the CDLB96 [McKeith *et al*. 1996], later updated to the CDLB05 criteria [McKeith *et al*. 2005]. In these criteria, LBD diagnosis is based on the extent of LB and Lewy neurites. In the CDLB96 criteria, the presence of LB in the brainstem was sufficient for LBD diagnosis, regardless of concomitant Alzheimer or other pathology, while in the CDLB05, LB in at least the limbic structures in the absence of severe AD is required for the consideration of LBD as diagnosis. Furthermore, a neuropathological staging system for PD has been presented by Braak and co-workers (hereafter referred to as Braak PD) [Braak *et al*. 2003]. This system, based on the extent of LB and Lewy neurites as well, may also be used as criteria for LBD.

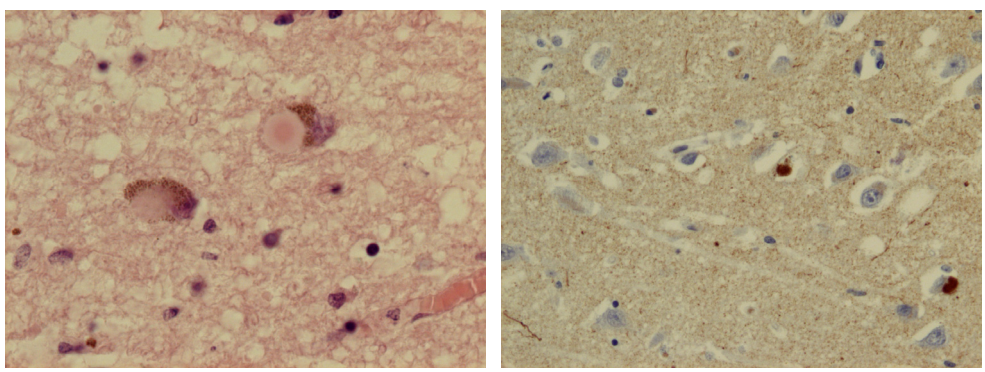

Figure 3*. Common histopathological findings in Lewy body disease. Lewy body in pigmented neuron of the substantia nigra. Haematoxylin-eosin staining, x40 objective (**left**). Cortical Lewy bodies and Lewy neurites. Immunohistochemical staining for α-synuclein, x20 objective (**right**).*

The neuropathology of frontotemporal lobar degeneration

Pathological features: FTLD is a heterogeneous family of neurodegenerative diseases. Common to all FTLD subtypes is a macroscopic frontal and/or temporal lobe atrophy, which may be in the range mild to severe, and the presence of microscopic neurodegenerative features such as neuronal shrinkage and loss, micro-vacuolisation, gliosis, cytoarchitectural disorder, and often cortical atrophy and collapse. In areas with cortical degeneration, the underlying white matter tends to be affected, with the loss of myelin and axons. Apart from this, there are many differences between the FTLD subtypes. [Cairns *et al*. 2007; Lowe *et al*. 2008]

FTLD subtypes may be divided into 'tauopathies', 'TDP-43 proteinopathies', 'FUS proteinopathies' and other forms (see Table 3). The former have intracellular tau-positive silver-stainable inclusions (often called 'tangles', while some authors reserve the term 'tangles' for AD-related lesions), and include PiD, CBD, PSP and other less common subtypes. PiD typically presents with rather severe asymmetric frontal and temporal lobe atrophy, and quite often with atrophy of the basal ganglia. Microscopically, Pick cells and Pick bodies are seen, the former being ballooned neurons with eosinophilic cytoplasm and eccentric nucleus, and the latter tau-positive neuronal inclusions found in for example the dentate gyrus of the hippocampus. CBD typically presents with asymmetric frontal, central and sometimes parietal atrophy, as well as a varying degree of atrophy of the basal ganglia and depigmentation of the substantia nigra. The distinctive microscopic features are tau-positive inclusions in neurons and glial cells (including so-called astrocytic plaques and oligodendroglial coiled bodies) and tau-positive thread-like processes in the cortex, white matter and basal ganglia. Ballooned cortical neurons are also seen. PSP typically presents with mild frontal lobe atrophy, severe atrophy of the subthalamic nucleus, superior cerebellar peduncle as well as the midbrain and pontine tegmentum, and depigmentation of the substantia nigra. The globus pallidus may also be discoloured and the LC depigmented. The characteristic microscopic features include tau-positive globose tangle-like neuronal inclusions, tau-positive thread-like processes (mainly in the diencephalon and brainstem), and tau-positive glial pathology (including so-called tufted astrocytes and oligodendroglial coiled bodies). Tau-negative FTLD cases usually have neuronal inclusions positive for both ubiquitin/p62 and TDP-43. These cases present with a varying degree of atrophy of the frontal and temporal lobes and basal ganglia. The substantia nigra may also be affected. The microscopic hallmark features are the ubiquitin/p62- and TDP-43-positive thread-like processes and neuronal inclusions, the latter round or rod-shaped of varying size. FTLD cases with TDP-43-positive inclusions may exhibit skein-like, Lewy body-like and so-called Bunina body inclusions, together with motor neuron loss and corticospinal tract degeneration. These cases are associated with motor neuron disease (similar to amyotrophic lateral sclerosis), and are regarded as a separate FTLD subtype. Of the remaining FTLD cases, i.e., tau- and TDP-43-negative FTLD, the majority exhibit inclusions

positive for FUS and ubiquitin/p62 protein staining. Rarer subtypes may exhibit inclusions positive for ubiquitin/p62-staining only (TDP-43- and FUS-negative), or have no specific inclusions. [Cairns *et al*. 2007; Ince *et al*. 2008; Lowe *et al*. 2008; Kovacs & Budka 2010; Mackenzie *et al*. 2010; Urwin *et al*. 2010] Images of some common neuropathological findings in FTLD are seen in Figure 4.

Neuropathological criteria: In 1994, the Lund and Manchester groups presented a consensus statement including neuropathological criteria for FTLD [Lund and Manchester Groups 1994]. Later consensus statements have been presented by other international groups [McKhann *et al*. 2001; Cairns *et al*. 2007]. Basically, the cited FTLD criteria are based on the presence of neurodegeneration (including

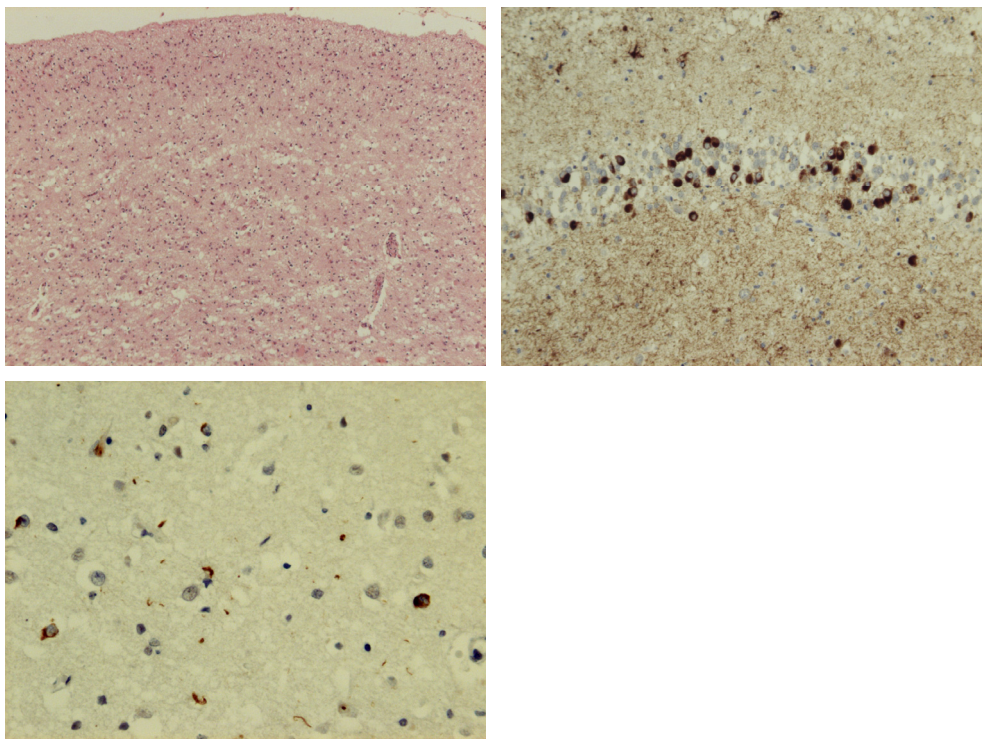

Figure 4*. Common histopathological findings in frontotemporal lobar degeneration. Severe cortical degeneration in the frontal lobe with loss of neurons, micro-vacuolisation, cytoarchitectural disorder and gliosis. Haematoxylin-eosin staining, x4 objective (**upper left**). Neuronal tau-positive inclusions in the dentate gyrus of the hippocampus (Pick bodies). Immunohistochemical staining for tau, x10 objective (**upper right**). TDP-43-positive neuronal inclusions and thread-like processes. Immunohistochemical staining for TDP-43, x20 objective (**lower left**).*

neuronal loss et cetera) in the absence of other neurodegenerative pathology such as AD and LBD. Especially the more recent criteria [McKhann *et al*. 2001; Cairns *et al*. 2007] have thoroughly addressed the issue of FTLD subtyping, based on protein inclusion pathology.

Neuropathological diagnostics studies

There are several methodological issues that may affect neuropathological dementia diagnostics (in turn affecting prevalence and concordance studies, as previously discussed). These issues may be divided into those relating to the neuropathological procedure, e.g., the selection of stains and brain areas for evaluation and laboratory staining quality, and those relating to neuropathological judgement, e.g., intra- and interrater diagnostic variability and differences in the use and interpretation of neuropathological diagnostic criteria and staging protocols.

In the literature, there are many studies addressing methodology in neuropathological dementia diagnostics, mainly in the field of AD. Concerning the choice of staining method, Braak staging of Alzheimer-related neurofibrillary pathology (described in detail later) may be performed using either a silver impregnation or an IHC staining for tau [Braak & Braak 1991; Braak *et al*. 2006a]. In the publication presenting IHC staining for Braak staging [Braak *et al*. 2006a], it is stated that, based on experience, there is a slight tendency to assign a higher stage when using IHC staining, something not seen in a later study from the BrainNet Europe Consortium [Alafuzoff *et al*. 2008a]. From the BrainNet Europe Consortium, two studies on inter-laboratory staining quality have also been presented, showing quite a variable quality for the Gallyas and Bielschowsky silver stains and IHC staining for β-amyloid and tau, both between and within different centres [Alafuzoff *et al*. 2006; Alafuzoff *et al*. 2008b]. The results from these studies are in favour of IHC stains, in comparison with conventional ones, from a reliability perspective. Furthermore, there are several studies on intra- and/or interrater reliability, showing that neuropathologists, regardless of staining method, do not exhibit perfect agreement when assessing Alzheimer [Paulus *et al*. 1992; Chui *et al*. 1993; Mirra *et al*. 1994; Nagy *et al*. 1997; Nagy *et al*. 1998c; Alafuzoff *et al*. 2008a; Alafuzoff *et al*. 2008b], CAA [Alafuzoff *et al*. 2009a] or Lewy-related pathology [Müller *et al*. 2005; Leverenz *et al*. 2008; Alafuzoff *et al*. 2009b]. In the cited studies, the kappa values were in the range of 0.19-0.98 and 0.61-0.97 for inter- and intrarater agreement, respectively (0 being no better than chance, and 1 being perfect agreement [Altman 1991]). Also, there are studies demonstrating that the use of different neuropathological criteria for Alzheimer [Geddes *et al*. 1997; Nagy *et al*. 1998a; Nagy *et al*. 1998b; Newell *et al*. 1999; Alafuzoff *et al*. 2008a] and Lewy-related pathology [Alafuzoff *et al*. 2009b], respectively, may result in different diagnoses in demented patients. In conclusion,

methodological issues do matter, but their actual importance in research and routine diagnostics is not fully clear.

Neuropathological staging in dementia

As previously mentioned, there are several neuropathological dementia subtype criteria. Many criteria are binary, i.e., significant pathology can be either present or absent. However, there are also neuropathological staging systems, in essence grading the pathology using an ordinal scale, e.g., from 'none' to 'severe'. Considering the clinical nature of dementing disorders with a decline in cognitive function over time, neuropathological staging systems probably reflect reality better than do binary criteria. Furthermore, many demented patients exhibit pathology of more than one type, mainly AD in combination with VaD or LBD [Petrovitch *et al*. 2005; Kovacs *et al*. 2008; Jellinger 2009]. In these cases, it may be difficult to determine which pathological components should be considered significant and concomitantly non-significant, respectively, and also to determine which component may have had the greatest impact on the cognitive decline. The use of staging systems, enabling a relative evaluation of different types of pathology, may be advantageous in this situation.

Staging in Alzheimer's disease

There are a few neuropathological staging systems for AD in the literature. The most commonly used internationally are the previously mentioned Braak [Braak & Braak 1991; Braak *et al*. 2006a], CERAD [Mirra *et al*. 1991] and NIA-RI scales [National Institute on Aging, and Reagan Institute Working Group 1997].

Braak: The Braak staging system is based on the topographic distribution of the neurofibrillary lesions NFT and neuropil threads [Braak & Braak 1991; Braak *et al*. 2006a]. The scale has seven stages, 0-VI. At Braak stage 0, there are no neurofibrillary lesions. At Braak stage I, neurofibrillary lesions involve only the superficial cellular layer pre-α of the transentorhinal region. At stage II, lesions are also found in the entorhinal pre-α and in the hippocampal sector CA1. At stage III, the lesions extend to the entorhinal pre-β, and may be seen in the amygdala and other limbic areas, while the isocortex is only minimally affected. At stage IV, there is involvement of the entorhinal pri-α and the temporal isocortex. At stage V, the lesions extend to the peristriate area of the occipital lobe, and at stage VI, the striate area is also affected. The stages can be grouped into the transentorhinal stages, the limbic stages and the isocortical layers, corresponding to stages I-II, III-IV and V-VI, respectively. In the original publication [Braak & Braak 1991], thick sections from polyethylene glycol-embedded blocks (seldom used in clinical

practice) stained with Gallyas silver staining were used. In the revision from 2006 [Braak *et al*. 2006a], the staging system was adapted to IHC staining for tau, with further clarifications on location of the tissue blocks needed for staging. A further modification of the Braak staging system has been proposed, with staging based only on the topographic distribution of neuropil threads (disregarding NFT) [Alafuzoff *et al*. 2008a], which may be seen as an entirely different staging system.

CERAD: The CERAD staging system is based on the semiquantitative assessment of NP frequency [Mirra *et al*. 1991]. The scale has four stages, 0-C. In short, the frequency of NP – graded none, sparse, moderate and frequent – is evaluated in three different areas: the middle frontal gyrus, the superior and middle temporal gyri, and the inferior parietal lobule. The frequency in the area with maximum involvement is related to the patient's age, generating the CERAD stage. For patients aged <50 years, sparse or more NP is classified as stage C. For patients aged 50-75 years, moderate or more NP is classified as stage C, and sparse as stage B. For patients aged >75 years, frequent NP is classified as stage C, moderate as stage B, and sparse as stage A. No presence of NP is always classified as stage 0, indicating no histological evidence of AD. CERAD stage A means histologically uncertain evidence of AD, while stage B suggests AD and stage C indicates AD.

NIA-RI: The NIA-RI staging system combines the Braak and CERAD grading scores, resulting in a likelihood rating for AD [National Institute on Aging, and Reagan Institute Working Group 1997]. The scale has four stages, no-high. According to the staging system, there is a high likelihood that the dementia syndrome is caused by AD in patients with Braak V-VI and frequent NP according to CERAD. Likewise, there is an intermediate likelihood for AD in demented patients with Braak III-IV and moderate NP according to CERAD, and a low likelihood in patients with Braak I-II and sparse NP. The CERAD grade, rather than the age-related CERAD stage, is used for the NIA-RI staging. In cases of disconcordance between Braak and CERAD stage, it has been proposed that the NIA-RI stage should be restricted by the lowest grade of Braak/CERAD [Jellinger 2009], which solves the problem with cases being unclassifiable due to unequal Braak and CERAD stages.

Staging in Lewy body disease

CDLB96/05: The CDLB96 [McKeith *et al*. 1996] and the revised CDLB05 criteria [McKeith *et al*. 2005] are staging systems for LBD. Both are based on semiquantitative assessment of Lewy-related pathology in several different brain regions. Depending on the pattern of pathology, cases are classified as no LBD, brainstem-predominant, limbic/transitional or diffuse neocortical LBD; thus, four

stages. The examined brain regions, the semiquantitative assessment procedure, and the rating of pathology differ to some extent between the CDLB96 and the CDLB05. A major difference, however, is the relative evaluation of Lewy-related vs. Alzheimer pathology in the CDLB05 [McKeith *et al*. 2005]. In essence, the CDLB05 stage is compared with the NIA-RI (or Braak) stage for a likelihood rating that the Lewy-related neuropathological findings will be associated with a DLB clinical syndrome. For example, the likelihood is low in a case with brainstem-predominant Lewy-related pathology and low or higher NIA-RI stage (Braak stage I or more), while the likelihood is high in a case with diffuse neocortical Lewy-related pathology and intermediate or lower NIA-RI stage (Braak stage IV or less). In order to simplify, increase interrater agreement and decrease the proportion of cases unclassifiable by the staging system, different modifications to the CDLB05 diagnostic procedure have been proposed [Ballard *et al*. 2006; Leverenz *et al*. 2008; Alafuzoff *et al*. 2009b]. In these modifications, a new stage has been presented, called amygdala-type LBD, characterised by Lewy-related pathology either in the amygdala only or in excess in the amygdala.

Braak PD: The Braak PD staging system [Braak *et al*. 2003] is also applicable in LBD. The scale has seven stages, 0-6, based on the topographic distribution of Lewy-related pathology. At Braak PD stage 1, Lewy-related pathology is found only in the dorsal motor nuclei of cranial nerve IX and X and/or the intermediate reticular zone of the medulla. At stage 2, pathology is also found in the pons, including the LC and raphe nucleus. At stage 3, the pathology extends to the substantia nigra in the mesencephalon and the nucleus basalis of Meynert. At stage 4, the transentorhinal region, the amygdala and the hippocampal sector CA2 are involved. At stage 5 and 6, the neocortex is affected, at stage 6 also including first order sensory association areas and premotor areas. Modifications to the Braak PD diagnostic procedure have been proposed as well [Müller *et al*. 2005; Alafuzoff *et al*. 2009b].

Staging in vascular dementia and frontotemporal lobar degeneration

Neuropathological staging systems for VaD and FTLD are rare, and no widely accepted systems or consensus statements exist. In a study addressing vascular and Alzheimer pathology in PD and LBD, Jellinger and Attems [Jellinger & Attems 2008b] graded vascular pathology in four stages, 0-3, based on the presence and extent of CAA, white matter lesions, large infarcts, lacunes, micro-infarcts and hippocampal sclerosis. Also, Broe and co-workers [Broe *et al*. 2003] presented a neuropathological staging system for FTLD with five stages, 0-4, based on the macroscopic degree of atrophy in the frontal and temporal lobes, basal ganglia and thalamus, and widening of the ventricles.

Staging studies

Concordance and differences between neuropathological staging systems have been addressed in a few studies. The Braak, CERAD and NIA-RI staging systems for AD [Braak & Braak 1991; Mirra *et al*. 1991; National Institute on Aging, and Reagan Institute Working Group 1997; Braak *et al*. 2006a] have been compared in systematic studies [Geddes *et al*. 1997; Newell *et al*. 1999; Alafuzoff *et al*. 2008a], and in studies on dementia-related pathology in normal aging and MCI [Hulette *et al*. 1998; Knopman *et al*. 2003b; Bennett *et al*. 2005]. The CDLB05 and Braak PD staging systems for LBD [Braak *et al*. 2003; McKeith *et al*. 2005] have also been compared with each other [Alafuzoff *et al*. 2009b]. The cited studies indicate that the concordance between staging systems is not perfect. Hence, the choice of staging system may affect the reporting of neuropathological severity and final diagnosis. Also, differences in the extent of NFT and NP, assessed with the Braak and CERAD staging systems, respectively, are not uncommon in cases with Alzheimer pathology, which may be of interest from a pathogenetic perspective.

To achieve a valid neuropathological staging system, the clinical and pathological dementia grade should correlate in a meaningful way. Logically, it may be advantageous to use the neuropathological staging system with the best correlation for each dementia subtype. Investigations have shown that NFT density and Braak stage correlate significantly with cognitive function in elderly. Plaque density, on the other hand, exhibits a correlation with cognitive function only in a few studies; generally, the correlation is better for NP than plaques all types. However, the correlations are far from perfect, and patients with practically no NFT may still have clinically severe dementia judged to be caused by AD, while patients with quite an extensive amount of NFT and/or plaques may still not be clinically demented. [McKee *et al*. 1991; Price *et al*. 1991; Arriagada *et al*. 1992; Bancher *et al*. 1993; Bierer *et al*. 1995; Nagy *et al*. 1995; Grober *et al*. 1999; Nelson *et al*. 2007] A correlation between pathological and clinical dementia grade has also been shown in LBD. However, as for Alzheimer pathology, the correlations are not perfect, and normal cognitive status is not uncommon in cases with neocortical LB. [Braak *et al*. 2006b; Aho *et al*. 2008; Parkkinen *et al*. 2008] In conclusion, it has not been possible to identify a cut-off level for neuropathological load to cause dementia, either for Alzheimer or Lewy-related pathology [see also: Jellinger 2006]. However, it should be noted that there are several difficulties with studies addressing clinical vs. pathological grading. Ideally, the study population should be cognitively well-examined within a short time before death, and pathologically pure subtypes (i.e., not cases with mixed pathology) must be used to study the impact on cognition by a single type of disease. Furthermore, medication and somatic diseases may influence cognitive function in patients, something not easily corrected for, which may affect the outcome of such studies. Thus, it is possible that the clinical and pathological grades correlate better than is known, and to an acceptable degree, in the existing staging systems.

Present investigation

Aim

The overall aims of the papers constituting this thesis were to investigate aspects of neuropathological findings in patients with dementia and neuropathological staging of dementia disorders, the future gain hopefully being increased epidemiological knowledge and improved neuropathological – and ultimately clinical – dementia subtype diagnostics. More specifically, in study I, the aim was to investigate the prevalence of dementia subtypes, based on neuropathological findings, in a population as similar as possible to the general population of demented patients. In study II, the aim was to examine neuropathological findings in relation to clinical diagnosis, i.e., the clinicopathological diagnostic concordance of dementia subtypes, in a broad population of demented patients. In study III, the aim was to investigate neuropathological locus coeruleus degeneration in different dementia subtypes. In study IV, the aim was to compare four different neuropathological staging systems for AD. In study V, the aim was to investigate neuropathological staging in LBD.

Study I

Methods

In this study, we included all patients with clinical dementia that upon death underwent a complete autopsy including neuropathological examination within the Department of Pathology, Lund, during the years 1974-2004. Patients with no neuropathological lesions were excluded. The neuropathological dementia subtype diagnoses were retrieved from the original reports.

Results

Of the 524 patients included, the neuropathological diagnosis was AD in 220 (42%), VaD in 124 (24%), AD+VaD in 113 (22%) and FTLD in 21 (4%) of the individuals. The remaining 46 (9%) cases had other dementia disorders, including dementia partially or fully caused by trauma, tumour, CJD, renal insufficiency with haemodialysis, alcohol abuse, multiple system atrophy, et cetera, and also including cases with mixed pathology and unresolved cases. The presence of LB

in the brainstem, limbic and/or neocortical areas was reported in 9.4% of the 524 patients, but only a single patient was diagnosed with pure LBD with no other significant concomitant pathology.

Comments

As in other consecutive autopsy studies on demented patients or investigations on similar populations (see Table 4 in the Background section of the thesis), AD was the most prevalent dementia subtype in our study. However, our results revealed a rather high frequency of VaD and AD+VaD. This may be due to the use of whole coronal and hemispheric brain sections at our department, which enables evaluation of large areas, advantageous in the assessment of vascular lesions, which are often multi-focal. On the other hand, the frequency of LBD was remarkably low in our study. One reason for this was that Swedish patients with PD/PDD are handled within the Department of Neurology and not at memory clinics, and referral for autopsy is quite rare from the former in our reception area. Another reason was that the IHC stain for α-synuclein protein was not used during all the covered years (introduced in Lund in 1999), and LB may be difficult to detect without this stain, at least in limbic and neocortical areas. A third reason was that only cases with LB as the sole pathological finding were diagnosed as LBD, while cases with, e.g., LB and concomitant Alzheimer pathology, were classified as AD. The frequency of FTLD in our study was similar to that of other studies, but lower than previously reported in Lund – the Lund Longitudinal Dementia Study [Brun & Gustafson 1993]. However, in the previous study, dementia cases from peripheral sites, neuropathologically investigated in Lund (with autopsy at a different hospital), were included, and among these cases there was a high frequency of FTLD. Based on the results of our and other similar studies (see Table 4 in the Background section of the thesis), it seems reasonable to conclude that pure AD should constitute about 40-50% of the cases in the demented population, VaD and AD+VaD about 15-20% each, LBD 5-10%, FTLD 2-4% and other dementia disorders 5-10%.

Study II

Methods

In this study, we included all patients with a clinical dementia disorder diagnosed at a memory clinic that upon death underwent neuropathological examination within the Department of Pathology, Lund, during the years 1996-2006. The clinical and neuropathological dementia subtype diagnoses were retrieved from the medical and pathological reports, respectively.

Results

In 86 (49%) of the 176 included cases, the clinical and neuropathological dementia subtype diagnoses were in full accordance. In an additional 24 (14%) cases, the clinical diagnosis corresponded with some but not all neuropathological components. The chance-corrected kappa value for diagnostic agreement was 0.37. For AD, the sensitivity and specificity (clinical AD to detect pathological AD alone or in combination with other pathology) were 46% and 88%, respectively. The corresponding values for VaD were 43% and 86%, for LBD 33% and 98%, and for FTLD 69% and 95%, respectively.

Comments

In our study, the clinicopathological dementia subtype diagnostic agreement was far from perfect, also true for other similar studies. In comparison with other investigations (see Table 6 and 7 in the Background section of the thesis), a somewhat lower sensitivity and higher specificity for AD diagnostics were seen in our study, while a slightly higher specificity and both lower and higher sensitivity for VaD have been presented in other studies in comparison with ours. The sensitivity for LBD was rather limited in our study, but the LBD group was quite small, making the figures uncertain (in contrast to Study I, Lewy-related pathology was here regarded in accordance with the CDLB05 [McKeith *et al*. 2005]), while the clinicopathological FTLD diagnostic concordance was rather good. Still, the results of our study show that the clinicopathological concordance in dementia diagnostics may be improved. In addition to the main result, the study also revealed that mixed pathology is common in demented subjects, especially in patients aged 75 years or older (in this group >60% exhibited mixed pathology).

Study III

Methods

In this study, we included all patients with clinical dementia that upon death underwent neuropathological examination within the Department of Pathology, Lund, during the years 1996-2008. Cases with no horizontal section of the pons including the LC at mid level were excluded. The neuropathological dementia subtype diagnoses and the macroscopic appearance of the LC were retrieved from the original reports. The microscopic appearance of the LC was evaluated for each case, using a previously developed scoring system for LC degeneration assessment, based on loss of neurons, neuronal loss of pigmentation, and extraneuronal pigment depositions (scores in the range 0-9 points).

Results

Among the 200 cases included in the microscopic evaluation, the highest average microscopic LC degeneration score was seen in the LBD group, followed by cases with AD and AD+VaD. The LBD and AD groups had significantly higher degeneration scores than the cases with AD+VaD, VaD, FTLD and the heterogeneous group of other dementia disorders. A cut-off score of 5 points was identified as the best for separation of LBD, AD and AD+VaD from the rest of the cases (sensitivity 84%, specificity 76%). The 43 patients with moderate or severe AD had a significantly higher LC degeneration score than the 24 patients with mild AD, while the LC degeneration scores did not differ significantly between the 25 patients with LBD (all with neocortical LB) and the 37 patients with LB confined to the brainstem (all with other concomitant pathology and not classified as LBD). The macroscopic appearance of the LC was described for 149 cases. The microscopic LC degeneration scores for the patients with macroscopically pathological LC (i.e., pale or not seen) were significantly higher than for the group with macroscopically normal LC. In 63 of the 74 cases (85%) with a macroscopic pathological LC, the dementia diagnosis was LBD, AD or AD+VaD.

Comments

The general LC degeneration seen in AD and LBD in our study was in adherence with results of other investigations [Jellinger 2003; Lyness *et al*. 2003]. Evaluation of the LC using a single horizontal section, as performed in our study, is easily manageable and suitable in routine diagnostics, and has been reported to be valid for the assessment of LC degeneration [Marcyniuk *et al*. 1986; Mountjoy & Bondareff 1986]. Also, the microscopic LC degeneration scoring system used in our study proved to be reliable based on the intrarater agreement between three independent researchers (weighted kappa 0.83-0.91). The macroscopic findings correlated well with the microscopic results of our study, but only the loss of neurons (not neuronal loss of pigmentation or presence of extraneuronal pigment depositions) correlated significantly with macroscopic LC degeneration. However, microscopic neuronal loss scoring did not separate the LBD, AD and AD+VaD cases from the rest of the study group as well as did total LC degeneration scoring. Macroscopic evaluation of the LC may be valuable in the preliminary dementia diagnostic procedure; in cases with macroscopic LC degeneration and concomitant cortical atrophy, AD should be suspected, while in cases with macroscopic LC degeneration without prominent atrophy, LBD should be suspected. The few cases with VaD and FTLD (of different subtypes, both tau-positive and tau-negative) that exhibited LC degeneration is an interesting finding, which, along with the actual implication of LC degeneration in AD and LBD, needs to be further examined.

Study IV

Methods

In this study, we included 43 consecutive patients with a clinical dementia disorder diagnosed at a memory clinic that upon death underwent neuropathological examination within the Department of Pathology, Lund, during the years 2002-2006. The patients were identified from the population investigated in Study II. Cases with FTLD and CJD were excluded, as were cases with stored material insufficient for AD staging. The Alzheimer pathology was evaluated for each case using the four neuropathological staging systems Braak [Braak & Braak 1991; Braak *et al*. 2006], CERAD [Mirra *et al*. 1991], NIA-RI [National Institute on Aging, and Reagan Institute Working Group 1997] and the Poly-pathology Alzheimer's disease assessment, nine areas (PPAD9), the latter based on the extent of neuronal degeneration, micro-vacuolisation, cytoarchitectural disorder, gliosis, neurofibrillary tangles and neuritic plaques, in nine cerebral regions.

Results

The four staging systems correlated significantly with each other when compared pair-wise using Spearman's coefficient of rank correlation (all p=0.003 or lower). The Spearman's rho value for PPAD9 vs. Braak was 0.65, for PPAD9 vs. CERAD 0.72, for PPAD9 vs. NIA-RI 0.67, and for Braak vs. CERAD 0.46. Rho values for the interdependent Braak vs. NIA-RI and CERAD vs. NIA-RI were 0.83 and 0.69, respectively.

Comments

In our study, there was a significant correlation between the four investigated neuropathological staging systems for AD, but the concordance was not perfect, indicating differences in procedure and targeted pathology between the systems. Hence, the choice of staging system will affect the evaluation of Alzheimer pathology and ultimately the neuropathological diagnosis. The PPAD9 staging system is a development of the original scale by Brun and Englund [Brun & Englund, 1981]. The system takes into account several morphological alterations that are seen in AD. As some features are semiquantitatively assessed, the scale may have a greater risk of subjective influence, although this was contradicted in our study by a rather good intra- and interrater agreement (weighted kappa 0.89 and 0.87, respectively). Also, while covering more brain areas, larger tissue sections are needed for PPAD9 staging. The Braak, CERAD and NIA-RI staging systems are easy to use. The former two rely on a single type of morphological alteration (NFT and NP, respectively), which may make the evaluation vulnerable

to atypical cases. The NIA-RI system, on the other hand, is based on both Braak and CERAD. All three systems rely on a single type of staining. Gallyas silver staining, used for visualisation of NFT and NP in our study, proved to be satisfactorily reliable, but may have an influence on judgement of neurofibrillary lesions in odd cases. The correlation between CERAD and Braak staging was slightly better when not relating the frequency of NP to the patient's age (rho value 0.63) – which is the basis for the NIA-RI system – but a substantial number of cases did not perfectly fit the NIA-RI categorisation in our study nevertheless.

Study V

Methods

In this study, we prospectively included 36 consecutive patients with a clinical dementia disorder that upon death underwent neuropathological examination within the Department of Pathology, Lund, during the period December 2008 to April 2010. Cases with CJD were excluded. At the time of analysis, 12 of the cases were available for evaluation. LB pathology was assessed in each case, with application of several staging systems for LBD, including the three-stage CDLB05 system and the six-stage Braak PD system and modifications of these scales [Braak *et al*. 2003; McKeith *et al*. 2005; Müller *et al*. 2005; Ballard *et al*. 2006; Leverenz *et al*. 2008; Alafuzoff *et al*. 2009b] (also including our own system, based on CDLB05).

Results

Half or more of the 12 included cases were not classifiable by the Braak PD and CDLB05 systems and by the system of Ballard and co-workers [Braak *et al*. 2003; McKeith *et al*. 2005; Ballard *et al*. 2006]. Diagnostic concordance was calculated for the staging systems with no unclassifiable cases. Weighted kappa (quadratic weights) was used for diagnostic agreement between different three-stage systems and different six-stage systems, respectively, with values in the range of 0.89-0.94. Spearman's coefficient of rank correlation was used for correlations between three- and six-stage systems, with rho values in the range of 0.83-1.0.

Comments

If applied strictly, a substantial part of the cases included in this study were not classifiable using some of the staging systems, limiting the usefulness of these systems. On the other hand, the concordance in staging was rather good between

the systems with no unclassifiable cases. Still, the choice of staging system may affect the stage of Lewy-related pathology and, ultimately, the final diagnosis. In this study, 12 different areas were evaluated for the presence of Lewy-related pathology in each case, in order to perform the staging according to each system. It does not seem necessary to examine all these regions. IHC staining for α-synuclein on a couple of areas of the brainstem, limbic structures and the neocortex should be sufficient.

Conclusions study I-V

We confirm that AD is the most common dementia subtype, followed by VaD and AD+VaD (in our material 42%, 24% and 22% of the cases, respectively).

Mixed pathology is common in dementia, especially in the oldest patients.

Clinicopathological agreement in dementia subtype diagnostics is not perfect (not more than 63% in our material) and may hopefully be improved.

LC degeneration, often already seen macroscopically, generally indicates the diagnoses LBD and AD among demented patients, while a preserved LC occurs mainly in VaD and FTLD.

Various neuropathological AD staging systems differ in procedure and targeted pathology, and the choice of system affects the judgement of Alzheimer pathology and hence the final diagnosis.

The PPAD9 system is from a histopathological perspective the most comprehensive staging system for AD of those investigated, but it remains to be systematically evaluated against cognitive status.

Various neuropathological LBD staging systems differ in applicability and also to some extent in judgment of Lewy-related pathology.

Until the validity of different neuropathological staging systems has been further studied, we suggest the use of more than one staging system for AD and LBD, respectively.

Populärvetenskaplig sammanfattning på svenska (General summary in Swedish)

Demens är ett syndrom som kännetecknas av tillkommen och bestående nedsättning av kognitiv förmåga (inklusive minne och andra funktioner såsom språk, logiskt och abstrakt tänkande, igenkänning, förmåga att utföra komplexa handlingar med mera), där nedsättningen är tillräcklig för att påverka personens vardagliga liv. För att kunna ställa diagnosen demens är undersökning av en person i livet nödvändig. Dock finns det ett stort antal sjukdomar som kan orsaka demens, och för att med säkerhet kunna säga vilken demenssjukdom en person lider av krävs en så kallad neuropatologisk undersökning, där man efter döden undersöker hjärnan med hjälp av mikroskop. Denna avhandling har sin utgångspunkt i neuropatologin, och har som övergripande mål att studera neuropatologiska skador/sjukdomar hos dementa samt neuropatologisk gradering av demenssjukdomar.

Avhandlingens första delstudie syftade till att undersöka förekomsten av olika demenssjukdomar bland dementa. I studien inkluderades 524 patienter med demens som obducerats och genomgått neuropatologisk undersökning i Lund under åren 1974-2004. Alzheimers sjukdom var den vanligaste demenssjukdomen, och var ensam orsak till demenstillståndet i 42% av fallen. Därefter följde vaskulär demens (demens orsakat av upprepade stroke och/eller andra skador till följd av dålig blodcirkulation) och demens till följd av kombinerade Alzheimer-förändringar och vaskulära skador, vilka utgjorde drygt 20% av fallen vardera. Hos ungefär 4% av patienterna var orsaken så kallad frontotemporal demens. I knappt 10% av alla fall såg man förekomst av så kallade Lewy bodies vid mikroskopisk undersökning. Dock klassades Lewy bodies som orsak till demensen (så kallad Lewy body demens) endast hos en individ; i övriga fall fanns andra samtidiga sjukdomsförändringar som ansågs vara grunden för demensen.

I avhandlingens andra delstudie jämfördes klinisk demensdiagnos (ställd när patienten var i livet) med neuropatologisk demensdiagnos hos 176 patienter som i livet diagnostiserats på en minnesmottagning och efter döden genomgått neuropatologisk undersökning i Lund åren 1996-2006. Studien visade att klinisk och neuropatologisk diagnos stämde överens i 49% av fallen, medan den kliniska diagnosen stämde överens med en del men inte alla neuropatologiska skador eller sjukdomsförändringar i ytterligare 14% av fallen. Bäst överensstämmelse mellan klinisk och neuropatologisk diagnos såg man hos patienter med frontotemporal

demens, medan överensstämmelsen var något lägre för patienter med Alzheimers sjukdom, vaskulär demens och Lewy body demens.

I avhandlingens tredje delstudie undersöktes förlust av nervceller och andra sjukliga förändringar i en ansamling med pigmenterade nervceller i hjärnstammen kallad locus coeruleus. Studien inkluderade 200 patienter med demenssjukdom som genomgått neuropatologisk undersökning i Lund under åren 1996-2008. Studien visade att man i mikroskopet oftast ser sjukliga förändringar i locus coeruleus vid Alzheimers sjukdom (med eller utan samtidiga stroke eller andra vaskulära skador) samt vid Lewy body demens, medan locus coeruleus generellt är bevarad vid vaskulär demens och frontotemporal demens. Ofta går dessutom förlusten av nervceller att se för blotta ögat när man tittar på hjärnvävnaden, då locus coeruleus är blekare än normalt.

I avhandlingens fjärde delstudie jämfördes fyra olika neuropatologiska graderingssystem för Alzheimers sjukdom. Patienter som drabbas av Alzheimers sjukdom blir kliniskt som regel successivt sämre med fler och mer uttalade symtom. Även neuropatologiskt ser man en successiv försämring i sjukdomen med större spridning och ökad mängd sjukliga förändringar i hjärnan. Vid Alzheimers sjukdom ser man i mikroskopet ett antal olika sjukliga förändringar i hjärnvävnaden, såsom minskat antal nervceller, förekomst av så kallade tangles och plaques, vilket är sjukliga proteinansamlingar i respektive utanför nervceller, ökad mängd stödjeceller med mera. De olika neuropatologiska graderingssystem som används idag graderar efter olika av dessa mikroskopiska förändringar. Den aktuella studien visade att de fyra undersökta graderingssystemen stämmer måttligt väl överens, och att valet av graderingssystem kan påverka hur man bedömer graden av Alzheimerförändringar, vilket i sin tur kan påverka vilken demensdiagnos en patient får vid den neuropatologiska undersökningen.

I avhandlingens femte delstudie jämfördes på motsvarande sätt som i fjärde olika neuropatologiska graderingssystem för Lewy body demens. Här baseras samtliga befintliga graderingssystem på förekomst av samma typ av mikroskopiska sjukliga förändringar (dels rundade proteinansamlingar som kallas Lewy bodies och dels små trådlika förändringar som kallas Lewy neurites). Utifrån hur graderingssystemen är formulerade kunde en stor del av de undersökta patienterna inte graderas med tre av systemen. De övriga fem systemen klarade av att gradera samtliga patienter, och uppvisade god överensstämmelse vad gäller gradering. En viss skillnad sågs dock även mellan dessa fem system, vilket innebär att valet av graderingssystem kan påverka hur man bedömer graden av Lewy-relaterade förändringar, vilket i sin tur kan påverka vilken demensdiagnos en patient får vid den neuropatologiska undersökningen.

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