Criteria for the neuropathological diagnosis of dementing disorders: routes out of the swamp? *)

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Abstract: Dementia, defined as deterioration in several cognitive domains, is an issue of enormous medical and socio-economic significance, poised to become a public health problem. Mental impairment and dementia are not only caused by neuronal cell death/loss, but predominantly by dysfunction and loss of synapses causing a default neuronal network. Consensus criteria for both the clinical and neuropathological diagnosis of different types of dementias have recently been updated. Clinical diagnostic accuracy using revised research criteria and newly developed biomarkers (MRI, PET, CSF analysis, genetic markers) ranges from 65 to 96% (for Alzheimer disease), with a diagnostic specificity versus other dementias of 23-88%. Neuropathological assessment of dementing disorders using immunohistochemistry, molecular biologic and genetic methods can achieve a diagnosis/classification, based on homogeneous definitions, harmonized inter-laboratory methods and standards for the assessment of nervous system lesions, in almost 99%, without, however, being able to clarify the causes or aetiology of most of these diseases. Since there is considerable clinical, genetic, morphological and molecular biological overlap between many disorders associated with cognitive impairment, in particular neurodegenerative proteinopathies, the reliability and clinical relevance of neuropathological criteria need better qualification and validation in order to increase the accuracy and reproducibility of the diagnosis in these disorders. Although most of neurodegenerative dementing disorders are incurable at present, further prospective and concerted clinico-pathological studies using revised methodological and validated protocols are required to establish the nature, pattern and grade of lesions and thus to overcome the limitations of the current diagnostic framework. Data fusion may allow their uniform application and correlation with clinical data in order to approach a diagnostic "gold standard", and to create generally accepted criteria for differentiating cognitive disorders from healthy brain aging. Detection of disease-specific pathologies will be indispensable to determinate the efficacy of new therapy options.

Key-Words: dementia, diagnostic consensus criteria, neuropathology, biomarkers, Alzheimer disease, neurodegenerative disorders, mixed pathologies

*) In memory of Prof. H.G. Zapotoczky, Vienna, Graz, a pioneer of Austrian psychiatry, who died on July 3, 2010.

ISBN: 978-960-474-278-3

1 Introduction

Dementia (ICD-10 F00-F07), a term recently being under discussion [1,2], encompasses deteriorations in several cognitive domains [3-5]. Recently, it has been redefined as the differential manifestation of deteriorating brain functions over time as a part of aging due to cell deaths in the brain caused by neurodegeneration or any other disease [6]. However, due to recent research data, dementia is not only caused by neuronal cell death/cell loss [7,8], but predominantly by dysfunction and loss of synapses [9-12] that have been demonstrated in early AD [13] and in Lewy body diseases, eg, Parkinson disease [14], and by cholinergic neuronal and axonal abnormalities that also are present in aging and AD [15]. These changes cause disconnections of important nervous circuitries in a default network [16-20] that have been demonstrated *in vivo* in early AD [21].

Both the prevalence and incidence of dementia increase exponentially with age [22-28]. The risk of dementia at age 65-100 years for men is 33%, for women 45%. The prevalence of dementia of all causes increases between the 7th and 10th decade from 0.3-1.0% to 42.3-68.3%, its incidence from 0.8-4.0/1000 person/years (p/y) to 49.9-135.7/1000 p/y [29]; that of Alzheimer disease (AD) from 0.6 to 22.2% and of vascular dementia (VaD) from 0.2 to 5.2% [25] or from 0.2 to 16% over age 80 [30]. The prevalence for all dementias over age 85 ranges between 15% and 40% and their incidence between 60 and 100 person/years [31]. In people over age 90 years, the fastest growing segment in the US population, the prevalence of dementias was estimated as 28% in men and 45% in women, with doubling every 5 years only for women [32]. In the oldest-olds incidence of dementia continues to increase exponentially with age in both men and women up to 40.7% per year in the 100+ age group [33]. In USA, dementia prevalence increased with age from 5% in the 8th decade to 37.4% in those aged 95+ [34], while AD affects almost 50% of the adults over 85 years [35]. In Canada, it ranged from 2.4% to 34.5% between the 7th and 9^{t}h decade [36], and the prevalence of clinically diagnosed AD vs. VaD increased significantly after age 65 and was higher in the 85+ group than in the younger cohort [37]. In China, the prevalence of all dementias between the 7th and 10th decade increased from 2.5 to 34%. The prevalence for ages 65+ was 4.8% for AD and 1.1% for VaD, with age related increase of AD from 0.5-1% to 35%, while that of VaD after an increase up to 4% in the 9th decade rapidly decreased after age 90 yrs [38,39]. Dementia prevalence estimates vary widely within developing countries [40].

Worldwide, the number of demented persons in the year 2000 was estimated at 25 millions, rising to 55 millions in 2020 and almost 100 millions in 2050, representing 2.6% of the total and 6.2% of the active population in Europe [41]. About 46% of demented subjects live in Asia, 30% in Europe, and 12% in North America, while their proportion living in developing countries will increase to 70% by 2040 [42,43]. More impressive is the change in the ratio working versus demented people. In 2008 in Europe and China it was 69:1 and 230:1; in 2050 the relation will be 21:1 and 36:1, respectively (J. Attems, pers. com.).

With the disproportional growth of the elderly population, dementia is an issue of enormous socio-economic significance and has become an eminent public health problem. It causes a significant financial burden to society, estimated at 141 billion Euro per year for Europe and 422 billion US$ worldwide, including 34 to 56% for informal care [44,45].

Although established estimates of dementia in general and particularly in old aged persons are crucial for public health planning, prevalence and incidence rates above age 85 are imprecise and inconsistent because of lack of common diagnostic criteria, small numbers of very old individuals in most studies [46-49], and the fact that aged subjects with and without dementia show a high frequency of mixed pathologies and comorbidities [50-60]. On the other hand, "supernormal centenarians" showing preserved cognitive functions and minimal Alzheimer-type lesions may represent a rare phenotype relatively protected from age-related pathology [61-63].

1.1 Clinical assessment of dementia

Research and consensus criteria for the clinical diagnosis of the major dementing disorders exist and have recently been revised and updated, e.g., the NINCDS-ADRDA and DSM-IV-TR criteria for AD [3,64-66], Parkinson disease-dementia (PDD) [4,67], dementia with Lewy bodies (DLB) [68,69], frontotemporal lobe degeneration (FTLD) [70,71], VaD or vascular cognitive disorder (SCADDTD [72]; NINDS-AIREN DSM-IV [73-76], see [77]), mixed dementias [76-78], and others [79]. Diagnostic criteria were widely applied, establishing AD as the predominant cause of senile cognitive impairment, a course of action aptly referred to as "alzheimerization" of dementia [80]. Clinical cases with frontotemporal lobar degeneration also can be potentially identified antemortem by assaying levels of specific markers [81].

ISBN: 978-960-474-278-3

A recent review of 2861 neurodegenerative disease cases of the National Alzheimer's Coordinating Center (NACC) registry showed high diagnostic accuracy for AD (85% sensitivity, 51.1% specificity) and low diagnostic sensitivity for DLB (32% for pure AD and 12% for AD+DLB) with a specificity over 58% [82]. While the NINCDS-ADRDA criteria [65] combined with neuropsychologic assessment are still valid for 88-90% of AD [83], they do not exclude additional Lewy body and other pathologies [84]. PIB PET is specific for fibrillar Aβ molecular pathology but not for pathologic diagnosis of comorbid AD in individuals with PDD. The ability to specifically identify fibrillar Aβ in the setting of α-synucleinopathy makes [(11)C]-PIB PET a valuable tool for prospectively evaluating how the presence of Aβ influences the clinical course of dementia in patients with Lewy body disorders [85].

The clinical criteria for the diagnosis of VaD that are not interchangeable [86] showed an average sensitivity of 0.49 (range 0.20-0.89) and specificity of 0.88 (range 0.68-0.98) [87], with highest values for the Mayo Clinic criteria - sensitivity of 0.75 and specificity of 0.8 [88]. In an autopsy study of 110 demented patients aged 94.6±2.8 yrs (33% VaD, 24% AD, 44% mixed dementia), the diagnostic sensitivity and specificity of various criteria for VaD was 0.50-0.88 and 0.60-0.74, respectively [89]. Nondegenerative nonvascular causes of dementia are more common than expected. In a population-based clinical study, they involved 7.7% of patients with disease onset before the age of 70 years, and 5% of the older group [90]. Combination of clinical data with fusion of different biomarkers has already improved the clinical diagnostic accuracy of AD up to 96%, while their sensitivity and specificity versus other dementias is 23-88% [91,92]. A combination of the best CSF and MRI data will lead to a more precise diagnostic prediction [93,94], and will be further increased by using multimodal techniques and novel CNS biomarkers [20,95-97], but histopathology is still considered to add to premortem diagnostic accuracy [98].

The aim of this review is to discuss the diagnostic validity of currently used pathological criteria particularly of neurodegenerative dementias and their limitations as well as to give recommendations for future clinico-pathological research. The diagnosis and management of young-onset dementia presents challenges that differ from those of older patients. The burden of genetic disease in young-onset dementia is also higher than in late-onset dementia. Much of our understanding of the pathogenesis of the degenerative dementias has been driven by the identification of genetic mutations causing early-onset familial disease [99]

2 Value and pitfalls of pathological diagnostic criteria

At present, several diagnostic guidelines for the neuropathological diagnosis of most dementing disorders are used, relying on qualitative, semiquantitative, and topographic assessment of morphological and bio/histochemical sign posts, in particular specific protein inclusions in neurons, glia and other cells. A simplified molecular-pathologic classification of degenerative dementias is given in Fig. 1 (see also [100-102]). This will form the basis for their neuropathological diagnosis in the future. A multifactorial model for the neuropathological diagnosis of dementia in elderly subjects (Table 1) predicted dementia in only 76% of the cases in the population-based CFAS cohort, indicating the elevated frequency of pathologic changes in the brain of old non-demented subjects [50]. The approximate frequency of the most common forms of dementias according to several autopsy series are given in Fig. 2.

Neuropathological criteria for *Alzheimer disease*, in addition to cut-off quantitative values of senile plaques and tangles [103] and their semiquantitative assessment and age-adjustment in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) protocol [104], include the topographic staging of neuritic AD pathology [105], re-evaluated recently [106], the progress and distribution of Aβ deposition being different [105,107]. A growing body of evidence supports the idea that amyloid and neuritic plaques and NFTs actually define (but not fully represent) the disease process, which also involves neuroinflammation, synaptic, neuronal, and axonal dysfunction and loss. All these changes begin before significant cognitive decline occurs. The combination of the CERAD and Braak scores in the National Institute of Aging-Reagan Institute (NIA-RI) criteria relates dementia to AD-typical lesions with high, intermediate and low likelihood [108] (Table 2). These categories of AD diagnosis apply only to individuals with dementia, and the evaluation of the NIA-RI critera demonstrated their easy and rapid use in AD and nondemented subjects, but much less reliability for other dementing disorders. High Braak stages and CERAD criteria identified 54% and 97% of AD cases, respectively, and eliminated between 62 and 100% of nondemented ones with low Braak stages, whereas among non-AD neurodegenerative dementias only between 8 and 42% were identified (Table 3). A grading scheme of both tau and Aβ lesions within a cortical area was

proposed [115], while the International Classification of Diseases of the Nervous System (ICDNS) criteria were developed with the concepts of staging, grading and correlating with clinical data [116]. They might be supported by recent *in vivo* multitracer PET imaging of amyloid plaques and NFTs [94,117-121].

For *α-synucleinopathies*, in particular Lewy body disorders, in addition to assessment criteria [122], staging/classifiction systems based on the semiquantitative assessment of the distribution and progression pattern of α-synuclein (αSyn) pathology are used [123] that are suggested to indicate a predictable sequence of lesions [124,125]. They allow a distinction of three major phenotypes of LB disease - brainstem predominant, transitional/limbic and diffuse cortical [69,126,127] (Table 4), while AD with amygdala Lewy bodies is considered a distinct form of α-synucleinopathy [129]. Recent clinico-pathologic studies, although partly confirming these systems, have shown that between 6.3 and 47% of cases did not follow the proposed staging pattern of αSyn pathology [130-132]. On the other hand, 30-55% of elderly subjects with widespread/cortical αSyn pathology revealed no definite neuropsychiatric symptoms or were not classifiable [68,133-135]. Therefore, the criteria for categorization of Lewy-related pathology in patients with dementia had to be modified [68,134,135]. Neuropathologically proven DLB in the age group 85+ was common, but the clinical symptoms tended to associate better with severe tau (NFT) pathology than with extensive Lewy-related pathology [136]. PDD and DLB, sharing many clinical and morphological features and believed to form a continuum within the spectrum of LB diseases [69,123,130,137], have been shown to differ by more frequent LB affection of the hippocampal CA 2-3 subareas [130,138], and more severe diffuse amyloid load in the striatum of DLB [138,139], recently confirmed by *in vivo* studies using 11CPIB-PET [140,141], while others showed severe striatal Aβ deposition in both PDD and DLB [142]. The predictive value of striatal Aβ pathology with regard to cognitive impairment is still controversial [133]. Recent studies in postmortem brains of patients with PD and PDD revealed both elevated tauopathy and αSyn pathology in striata but no tau in frontal cortex [143].

In LB disorders, in particular PD and DLB, a multi-organ distribution of phosphorylated αSyn has been shown, with earliest involvement of the gastrointestinal tract and olfactory bulb [144].

Up to 50% of AD cases exhibit a third prevalent neuropathology: the aggregation of αSyn into Lewy bodies. Importantly, the presence of LB pathology in AD is associated with a more aggressive disease course and accelerated cognitive dysfunction. Recent studies confirmed that Aβ, tau, and αSyn interact synergistically *in vivo* (in both human and 3xTG AD mice to promote the aggregation and accumulation of each other and, thus, accelerate cognitive dysfunction [145].

For *frontotemporal lobe degeneration (FTLD)*, nowadays suggested to be the third or forth most frequent cause of dementias, criteria for neuropathological diagnosis are based on the basic biochemical markers [71,146-149] including the novel TDP-43 neurodegenerative proteinopathies [150], and a new subtype with FUS (fused in sarcoma gene) pathology [151], but there are cases with overlapping pathology [152]. However, FUS-immunoreactive intranuclear inclusions occur in various neurodegenerative diseases [153]. Recently, a small novel group of FTLD patients with clinical features that overlap with DLB has been identified, which morphologically were consistent with TDP-43 proteinopathy (FTLD with ubiquitin-only lesions, type I) [154,155]. A recent updated nomenclature for FTLDs is given in Table 5 [71]. FTLD in elderly patients presents features of several phenotypes and morphological subgroups similar to that seen in the presenile group, though patients with MAPT, but not progranulin mutations, or FUS pathology are rare or even absent [156].

For *vascular dementias* (or vascular cognitive impairment/diseases related to cerebrovascular pathologies), despite various proposals for a categorization of major cerebrovascular lesions [76,157] (Table 6, 7), a harmonization of the criteria and techniques for the assessment of cerebral lesions of presumable/possible vascular origin in cognitively impaired is necessary [159]. Due to the high variability of morphological findings and multifactorial pathogenesis of vascular cognitive impairment, no generally accepted morphologic scheme for quantitating cerebrovascular lesions and no validated neuropathological criteria for vascular dementia have been established to date (see [76,157,160]). The same holds for so-called "mixed dementia" [76,77]. Recently, BrainNet Europe II (BNE) has constituted a "vasculopathy" reference group to harmonize the assessment of vascular pathology similar to previous interlaboratory studies for the morphological assessment of AD-related and αSyn pathologies [106,122,127].

In contrast to most dementing conditions that typically develop over years, rapidly progressive dementia (RPD) being quickly fatal is one of the most challenging neuropathological problems. The differential diagnosis is often widely ranging, and in addition to frequent sporadic or genetic prion diseases includes rapidly progressing neurodegenerative tauopathies and

synucleinopathies, autoimmune condition infections, toxic-metabolic and neoplastic diseases [161,162]. According to the US National Prion Disease Pathology Surveillance Center (NPDPSC) in patients with RPD, treatable disorders are frequently mistaken for Creutzfeldt-Jakob disease (CJD). Among 1,106 brain autopsies, 32% were negative for prion disease; most frequent were AD (50%) and VaD (12%), while 23% were potentially treatable diseases, eg., immune-mediated, infectious disorders or tumors [163]. In these and other unclear conditions, brain biopsy may play a role, although frequently biopsy findings in dementia are non-specific [164,165].

3 Specific problems in the diagnosis of Alzheimer disease

Histopathological examination of the brain establishes that AD-related lesions are present in sufficient densities to distinguish AD from age-related lesions and allows detection of other dementing disorders [166]. The current algorithms for the neuropathologic diagnosis of AD are based on assessment of plaques and tangles. Despite reasonable interrater agreement when using standardized criteria [127,167-173], no one set of histopathological criteria for AD has been uniformely accepted by neuropathologists [174]. These algorithms that only consider the classical "plaque and tangle" phenotype of AD do not recognize other subtypes. It should be emphasized that the brains of many cognitively impaired patients fall into neuropathologic diagnostic criteria that cannot be defined explicitely by the current consensus recommendations. The analysis of 1677 cases with antemortem diagnosis of dementia from the National Alzheimer's Coordination Registry showed that 82.4% fell into diagnostic "boxes" that are within the rubric of consensus recommendations, while the others were "atypical" cases falling outside these "boxes" [175].

The "plaque predominant" type with abundant amyloid plaques, no or very little neuritic pathology restricted to the hippocampus and abnormal phosporylated tau in neocortical pyramidal cells but lacking overt tangle formation, accounting for 3.5-8% of demented subjects over age 85 years [176-179]. Many of these cases are associated with cortical Lewy bodies representing a specific type of Dementia with Lewy bodies (DLB) [180]. The "tangle dominant dementia" (TDD) with tau pathology often restricted to the limbic system, absence of neuritic plaques and no or very little (diffuse) amyloid plaques and rare amyloid angiopathy, accounts for 5-7% of oldest olds. Since the neurofibrillary tangles in this type react with 3- and 4-repeat tau similar to those in classical AD, it should be considered as a subtype of AD, however, with different ApoE genotypes [51,52,181]. Furthermore, the Lewy body variant of AD, with cortical and subcortical Lewy bodies is a subtype of Lewy body disorders, often asssociated with severe AD pathology [180]. Standard metrics for tangles and neuritic plaques [104,108,170] are usually semi-quantitative and, according to the BrainNet Europe consortium, good agreement can be reached in the neuropathological diagnosis only when the lesions are substantial, e.g., when they have reached isocortical structures (Braak stage V-VI with absolute agreement 91%). By contrast, for mild lesions the agreement was poorer (Braak stage I-II, agreement 50%) [127], thereby limiting the ability to make accurate correlation of *antemortem* cognitive status and morphological findings [182].

Although the sensitivity and specificity of the NIA-RI criteria is suggested to be 90%, only 30 to 57% of the brains of patients with the clinical diagnosis of probable AD show "pure" AD pathology (Table 8). Thus, their predictive value may be reduced to 38-44% [187].

In a retrospective clinicopathological study of 1,700 demented elderly persons (66% female; MMSE score <20; mean age at death 84.3±6.0 years; 90% over age 70 years), AD-related lesions were present in 83.2%, but pure AD without other pathologies was present in only 42.0%, AD with other pathologies including mixed demetnia in 41.2%, vascular deemtnia in 12.8%, other disorders in 4.1%, and negative pathology in 0.9% [186].

Diffuse and neuritic plaques and some amounts of tau-positive neuritic pathology in the limbic system relatively frequently occur in cognitively normal elderly [50,112,114,187-195]. Although cognitively unimpaired subjects may show variable neocortical AD-related pathology [196,197], in general, the number of isocortical tangles correlates best with clinical dementia severity [198-204]. The pattern of gray matter loss associated with tangle pathology is an appropriate *in vivo* surrogate indicator of AD pathology [205]. The predictive value of widespread tau pathology (Braak stages V-VI) for dementia is high [133,176], while others found that both diffuse and neuritic plaques, rather than tangles in neocortical regions distinguish nondemented and AD subjects with high sensitivity and specificity [206]. However, there is considerable heterogeneity in morphology, extent and topographical distribution of Aβ deposits in brains with fully developed AD. The cortical Aβ burden usually does not correlate with disease duration and the stage of tau pathology [207].

ISBN: 978-960-474-278-3

Although correlations between cognitive deficits and the severity and extension of tau pathology and/or the Aβ load have been found, at least in those without superimposed other pathologies, the distinction between "physiologic" (in non-demented subjects) and pathologic aging (often but not consistently associated with cognitive decline) may be difficult. Furthermore, the suggestion that plaques and NFTs, the morphologic markers of AD, may "cause" this disorder is oversimplified and wrong, since accumulating evidence suggests that AD pathology represents effect rather than cause or at least a host response to injury, equaling adaptative or neuroprotective reaction [208,209]. Larger brain and hippocampal values were associated with preserved cognitive function during life despite a high burden of AD pathology, but the mechanisms that protect the elderly from AD are unknown [195] (see [210]).

4 Dementia in the oldest-old

Neuropathology of AD in dementia in the oldest-old differs considerably in both intensity and distribution from that in younger age groups [211-213]. Increased densities of neuritic plaques and NFTs are absent in demented patients over age 85-90 years [47,214-220], and there is considerable overlap in the pathologies found in the demented and non-demented patients [48-50,221]. On the other hand, by age 80-85 years, many nondemented subjcts may have substantial subcortical AD pathology [222], while others found significant positive correlation between the extent of dementia and senile plaque density ($p=0.011$), but not for the NFT density score ($p=0.076$) [223]. Recent studies suggest that dementia in the oldest-old (90+ years of age) is only modestly related to AD, while both cardiovascular and cerebrovascular pathology may cause cognitive impairment in most elderly subjects with low Alzheimer pathology scores [160,182,186,224], and cerebrovascular lesions may contribute to the clinical expression of dementia [225]. However, there may be no evidence for a certain number of elderly subjects having dementia without an apparent causative morphologic background [186,226], although dementia lacking a known pathologic substrate is extremely rare [227].

In a retrospective clinicopathological study of 1100 elderly demented persons in Vienna, Austria (66% females, MMSE <20; mean age at death 83.3±5.4 SD years, 90% over age 70 years) AD pathology was seen in 84% ("pure" AD 42.9%, AD + other pathologies 41.1%), VaD in 10.8%, mixed dementia (AD + vascular encephalopathy) in 5.5%, and other disorders in 5.3% (Fig. 3). AD increased from the 7th to 10th decade from 32.2 to 45.1% with highest incidence in the 8th and 9th decade, and slightly decreased after age 90, while the relative prevalence of both AD + minor cerebrovascular lesions and mixed dementia significantly increased with age (7.8 to 32.9% and 0 to 7.%, respectively, $p<0.001$). By contrast, VaD showed a continuing age-related decrease from 15.6 to 9.4% ($p<0.05$), whereas AD + Lewy pathology remained fairly stable (10.3 and 11%) (Fig. 4) [228]. In a prospective study of 180 demented patients (mean age 85±3.4 years), autopsy showed AD in 48%, AD with vascular pathology in 19%, vascular dementia in 11%, dementia with Lewy bodies in 9%, and dementia of unknown etiology in 13% (KA Jellinger, unpublished observations).

A high percentage of demented persons aged 80+ do not met the pathological criteria of AD or were classified as "dementia of unknown etiology" [229,230]. Although clinico-pathological studies have shown that there are many important contributory causes to cognitive declinie in old persons, neuritic plaques and, more importantly, neurofibrillary tangles show statistically significant correlations with the severity of cognitive decline across age groups including patients older than 90 years, at least in those without superimposed other brain diseases [202,204].

5 The importance of confounding pathologies

An important problem is the frequent presence of confounding processes in the aged brain that coexist with AD, as cerebrovascular disease, Lewy body pathology, argyrophilic grain disease, hippocampal sclerosis, and so forth, with about two-thirds of aged human brains containing non-Alzheimer disease-type neuropathology [56,202,231], which have, however, frequently been missed clinically and could not be identified without neuropathological examination using modern biochemical and molecular-biological analyses. The frequency of mixed pathologies in demented elderly is shown in Table 8, and was recently confirmed in over 3300 autopsy cases of aged demented individuals [53]. Since 50 to 85% of the brains of persons who die aged 80-90+ old show appreciable cerebrovascular lesions [54], a specific problem is the impact of cerebrovascular disease in relation to AD pathology [232-237]. In several autopsy series of oldest old patients, the frequency of AD ranged from 12 to 66%, that of VaD from 9 to 46.8%, that of DLB between 9 and 24%, and that of mixed pathologies between 2 and 86% (!), and was over 40% in a large autopsy series of patients over age 80 [186].

ISBN: 978-960-474-278-3

The burden of vascular and AD type lesions are considered to be independent of each other, and are consistent with an additive or synergistic effect of both types of lesions on cognitive impairment [78,174,225,238-240]. The thresholds for vascular and degenerative lesions in distinguishing "pure" VaD or AD from mixed cases have been critically discussed [241-243]. AD pathology alone more frequently accounts for dementia than both microscopic and macroscopic infarcts [244], and in advanced or full-blown stages of AD concomitant small vascular lesions do not significantly influence the overall state and progression of cognitive decline, the severity and extent of AD pathology overwhelming the effects of cerebrovascular disease [157,160,232,245]. Nevertheless it should be borne in mind that all additional pathologies may interact, although their mutual impact often remains unclear. Therefore, the reliability and clinical relevance of the current diagnostic criteria need better qualification and validation. In addition, considerable phenotypical and morphological differences exist between genetic/familial and sporadic AD [210,246-248]. The synergistic interaction between Aβ, tau, and αSyn, accelerating neuropathology and cognitive decline, has been mentioned above.

Although molecular genetics, biochemistry and animal models, at least in part reproducing the morphology of human AD and related disorders, have produced a large and convincing body of data on the pathogenesis and pathophysiology of the disease, showing a complex cascade of events leading from preclinical to fully developed neurodegeneration, both their molecular backgrounds, basic etiologic factors, pathogenic interrelations and impact for the manifestation of AD are not yet fully understood.

6 Conclusions and future perspectives

There is increasing use of biochemical, genetic, and experimental approaches for refinement of diagnosis and analysis of the relevant contribution of different disease processes to neurodegeneration of AD and other dementias [1,3,16,18]. Since the majority of degenerative dementing disorders are associated with intracellular and/or extracellular deposition of misfolded proteins (proteinopathies), most of them can be classified and diagnosed by morphological, immunohistochemical and/or molecular-biological (neurochemical) identification of these deposits representing characteristic markers and signposts of particular disorders. Algorithms for the molecular-pathological classification of sporadic (nongenetic/nonhereditary) forms of neurodegenerative dementias have been proposed recently [100-102]. However, due to variable overlap, these changes may fail to distinguish between cognitively intact aged subjects from those with mild cognitive impairment (MCI) or preclinal or mild AD [198,249,250]. In particular these latter groups show a wide variety in the intensity and pattern of AD-related lesions. Although they often differ from "normal" aging, only a small proportion of cognitively intact aged are free of AD pathology, while up to 50% may show AD-related changes or even definite AD pathology [112,114,188-194]. Additional challenges arise from frequent coexistence with other pathologies that may have an additive or synergistic effect. Similar difficulties arise in other neurodegenerative dementias, in particular those with genetic background. The question, whether the neuropathological "gold standard is dead" has been discussed in respect to genetical neurodegenerative disorders that offer a rare opportunity to test the validity of neuropathological diagnostic criteria. There is currently no clinical "gold standard" and, occasionally, also no pathological "gold standard" for Parkinson disease (PD), while only the combination with genetic studies may provide definitive arbitration of validity of clinical and pathological diagnostic criteria [155,251]. Neuropathology using immunohistochemistry, molecular biological and genetic methods can achieve a diagnosis or classification in up to 99%, using homogenous and harmonized definitions and standardized inter-laboratory methods and standards for the assessment of nervous system lesions, and considering exact clinical data. International and interdisciplinary projects/initiatives for the standardized assessment of clinical, neuroimaging, biomarker, and neuropathologic data are currently under way [96,97,252-254]. In the majority of cases except those with known genetic or metabolic backgrounds, however, pathological examination may not be able to clarify the causes or aetiology of most dementing disorders, while some conservative authors emphasized that autopsy examination of well-studied cases of AD and other dementias still has a critical role to play [255]. Therefore, based on current knowledge and future research, "new" criteria for the neuropathological diagnosis of neurodegenerative and dementing disorders are needed in order to find a way out of the current "chaos" regarding histological diagnosis of dementia and their clinical implications [66,182]. Although molecular genetics, biochemistry and animal models, at least in part reproducing the morphology of human AD and related disorders, have produced a large and convincing body of data on the pathogenesis and pathophysiology of the disease and have made an increasing contribution to

postmortem studies of the cellular and molecular changes that underpin AD and other causes of dementia, the molecular backgrounds, the basic etiological factors, the pathogenic interrelationships of various concomitant pathologies need further validation. Harmonized techniques are required to increase the accuracy and reproducibility of neuropathological diagnosis as a basis for further successful treatment and neuroprotection – a long and difficult way out of the swamp.

Acknowledgements
The study was supported in part by the Society for the Promotion of Research in Experimental Neurology, Vienna, Austria. The author thanks Mrs. V. Rappelsberger for excellent laboratory work and Mr. E. Mitter-Ferstl, PhD, for secretarial and computer work.

Figure Legends
Figure 1. Molecular-pathologic classification of degenerative dementias.
Figure 2. Frequencies of the most common forms of dementia.
Figure 3. Frequency of neuropathologic diagnoses in the total cohort. AD Alzheimer's disease; CVD cerebrovascular dementia; VD vascular dementia; LBD Lewy body dementia; MIX mixed dementia (AD + cerebrovascular encephalopathy).
Figure 4. Age-related frequency of neuropathologic types of dementing disorders. AD Alzheimer's disease; CVD cerebrovascular dementia; LBD Lewy body dementia; VD vascular dementia; MIX mixed dementia (AD + cerebrovascular encephalopathy).

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ISBN: 978-960-474-278-3

ISBN: 978-960-474-278-3

Table 1. Multifactorial model for the neuropathological diagnosis of dementia [from 76]

Diagnostic elements
Age at death $P < 0.05$ <80 years vs. >80+ years
Brain weight $P < 0.09$ low for age vs. average/high for age
Neocortical senile plaques $P < 0.01$ not severe vs. severe
Neocortical tangles $P < 0.03$ not severe vs. severe
Limbic tangles $P < 0.19$ not severe vs. severe
Vascular lesions $P < 0.03$ no/single vs. multiple
Vascular amyloid $P < 0.01$ absent vs. present
Lewy bodies $P < 0.1$ absent vs. present

P values from the multivariate analysis are significant at <0.05.

Table 2. National Institute of Aging - Reagan Institute (NIA-RI) criteria for Alzheimer disease (AD)

	Braak neurofibrillary tangle stage			
CERAD senile plaque score	**No NFTs**	**I-II**	**III-IV**	**V-VI**
Frequent neuritic plaques	Not AD	Low	Interm.	High
Moderate neuritic plaques	Not AD	Low	Interm.	Interm.
Sparse neuritic plaques	Not AD	Low	Low	Low
No plaques	Not AD	Not AD	Not AD	Not AD

CERAD Consortium to Establish a Registry for Alzheimer disease; NFT neurofibrillary tangle, interm. intermediate.

Table 3. Likelihood of dementia (in percent) due to AD according to NIA-R-Institute criteria in various autopsy series

Author	Disorder	CERAD / Braak stage			Mean age (years)
		Low A / 0-II	Interm. B / III-IV	High C / V-VI	
Cochran et al. 1998 [109]	Demented (n=17)	47	41	12	?
	Non demented (n=40)	72.5	22.5	5	?
Newell et al. 1999 [110]	AD (n=33)	0	3	97	83
	DLB (n=15)	48	26	26	81
	PSP (n=12)	75	17	8	68
	Controls (n=17)	76	24	0	77
Harding et al. 2000 [111]	AD (n=31/22-no LB) (CDR 1-3)	26/13	20/27	54/60	77
	DLB, neocort. (n=11)	73	18	9	76
	PD (n=7) (CDR 0-0.5)	83	17	0	79
	Controls (n=18) (CDR 0-0.5)	83	17	0	79
Davis et al. 1999 [112]	Controls (n=57, MMSE 27-29)	88	-	12	84
McKee et al. 2002 [113]	AD (n=12) (CDR 1-3)	0	17	83	
	Cogn. normal (n=23) (CDR 0)	62	38	0	83
Jellinger 2006 [114]	AD (n=100) (MMSE 0-17)	0	24	76	85
	DLB (n=36) (MMSE 0-20)	25	33	42	77
	PSP (n=10)	70	20	10	72
	PD dem. (n=20, MMSE 0-20)	25	50	25	83
	PD non dem. (n=17, MMSE >20)	70	30	0	72
	Controls (n=20, MMSE 28-30)	100	0	0	81

CERAD Consortium to Establish a Registry for Alzheimer disease; AD Alzheimer disease; DLB dementia with Lewy bodies; PD Parkinson disease; dem. demented; PSP progressive supranuclear palsy; MMSE Mini-Mental State Examination score; CDR Clinical Dementia Rating scale.

ISBN: 978-960-474-278-3

Table 4. **BrainNet Europe protocol, i.e. assignment of the Braak stage and McKeith type of α-synuclein (αS) immunoreactive (IR) Lewy body (LB) disease related pathology as proposed by BrainNet Europe consortium.**

dmV Dorsal motor nucleus of vagus, _irx_ intermediate reticular zone, _LC_ locus coeruleus, _R_ raphe, _SN_ substantia nigra, _nbM_ nucleus basalis of Meynert, _AC_ amygdala, _CA2_ cornu Ammonis of hippocampus, region 2 _TOcx_ temporo-occipital cortex, _LN_ Lewy neurites.

Two to three regions represent each Braak stage. For a Braak stage only one of the required regions needs to be affected with the required (LB or LN) αS-IR pathology. For the McKeith brainstem type, one of the obligatory brainstem regions (medulla, pons, midbrain) has to be affected with LB and or LN. Only one of the two regions in Limbic or Neocortical type needs to be affected with the required (LB or LN) pathology. In Amygdala predominant type, the αS-IR LBs are either noted only in the AC or they are seen in excess in AC when compared to the brainstem regions. If occasional αS-IR LNs are seen in AC or in cortical regions without LBs, the case is assigned as a "+" case, i.e. a Braak stage 3+ or a McKeith brainstem +, when the case displays LBs and/or LNs up till midbrain but in addition LNs are seen in neocortical areas [from 128]

Sampled brain areas	Medulla		Pons		Midbrain	Basal forebrain		Hippocampus		Gyrus cinguli	Temporal cortex	Frontal cortex	Parietal cortex
Anatomical region	dmV	irx	LC	R	SN	nbM	AC	CA2	TOcx	grey matter	grey matter	grey matter	grey matter
Braak stage	1	1	2	2	3	3	4	3	4	5	5	6	6
McKeith type	BRAINSTEM					LIMBIC						NEOCORTICAL	
Amygdala predominant							AC predominant						
Lesion type requested	**LBs and / or LNs**						**LBs**	LNs	**LBs**				

Table 5. Updated nomenclature for frontotemporal lobar degeneration from Mackenzie et al 2010 [71]

2009 recommendation		2010 recommendation		
Major molecular class	**Recognized subtypes**	**Major molecular class**	**Recognized subtypes**	**Associated genes**
FTLD-tau	PiD	FTLD-tau	PiD	*MAPT*
	CBD	CBD		
	PSP	PSP		
	AGD	AGD		
	MSTD	MSTD		
	NFT-dementia	NFT-dementia		
	WMT-GGI	WMT-GGI		
	Unclassifiable	Unclassifiable		
FTLD-TDP	Types 1–4	FTLD-TDP	Types 1–4	*GRN*
	Unclassifiable		Unclassifiable	*VCP*
				9p
				(TARDBP)
FTLD-UPS	FTD-3	FTLD-UPS	FTD-3	*CHMP2B*
	aFTLD-U			
FTLD-IF	NIFID	FTLD-FUS	aFTLD-U	*(FUS)*
BIBD			NIFID	
			BIBD	
FTLD-ni		FTLD-ni		

ISBN: 978-960-474-278-3

Table 6. Newcastle categorization of the major CVLs associated with cognitive impairment [modified from 158]

VaD subtypes related to	**Newcastle subtype**
Large infarct or several infarcts (>50 ml); multi-infarct dementia	I
Multiple small or microinfarcts (>3 with minimum ∅ 5 mm); small vessel disease (involving greater than three coronal levels; hyalinisation, CAA, lacunar infarcts, perivascular changes, microhemorrhages). White matter lesions / leukoaraiosis / Binswanger disease	II
Strategic infarcts (eg, thalamus, hippocampus, basal forebrain)	III
Cerebral hypoperfusion (hippocampal sclerosis, ischemic–anoxic damage, cortical laminar necrosis, borderzone infarcts involving three different coronal levels)	IV
Cerebral hemorrhages (lobar, ICH or SAH)	V
Cerebrovascular changes with AD pathology (> Braak III); mixed dementia	VI

ISBN: 978-960-474-278-3

Table 7. Pathophysiological classification of VaD [modified from 158]

Large vessel dementia	Multiple infarct dementia (MID) Single-strategic infarcts (mesial-temporal, caudate and thalamus, fronto-cingulate, angular gyrus)
Small vessel dementia (sVaD)	Subcortical vascular dementia Binswanger subcortical encephalopathy Lacunar state CADASIL ‡, other hereditary angiopathies Collagen or inflammatory vascular diseases
Strategic infarct dementia (SID)	(Small) infarcts in functionally important brain regions (hippocampus, thalamus, frontal region)
Hypoxic/hypoperfusion dementia	Diffuse hypoxic-ischemic encephalopathy Borderline infarcts
Hemorrhagic dementia	Subdural hemorrhage Subarachnoid hemorrhage Intracerebral hemorrhage
Mixed dementia	Definitive AD + cerebrovascular disease

‡ Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

ISBN: 978-960-474-278-3

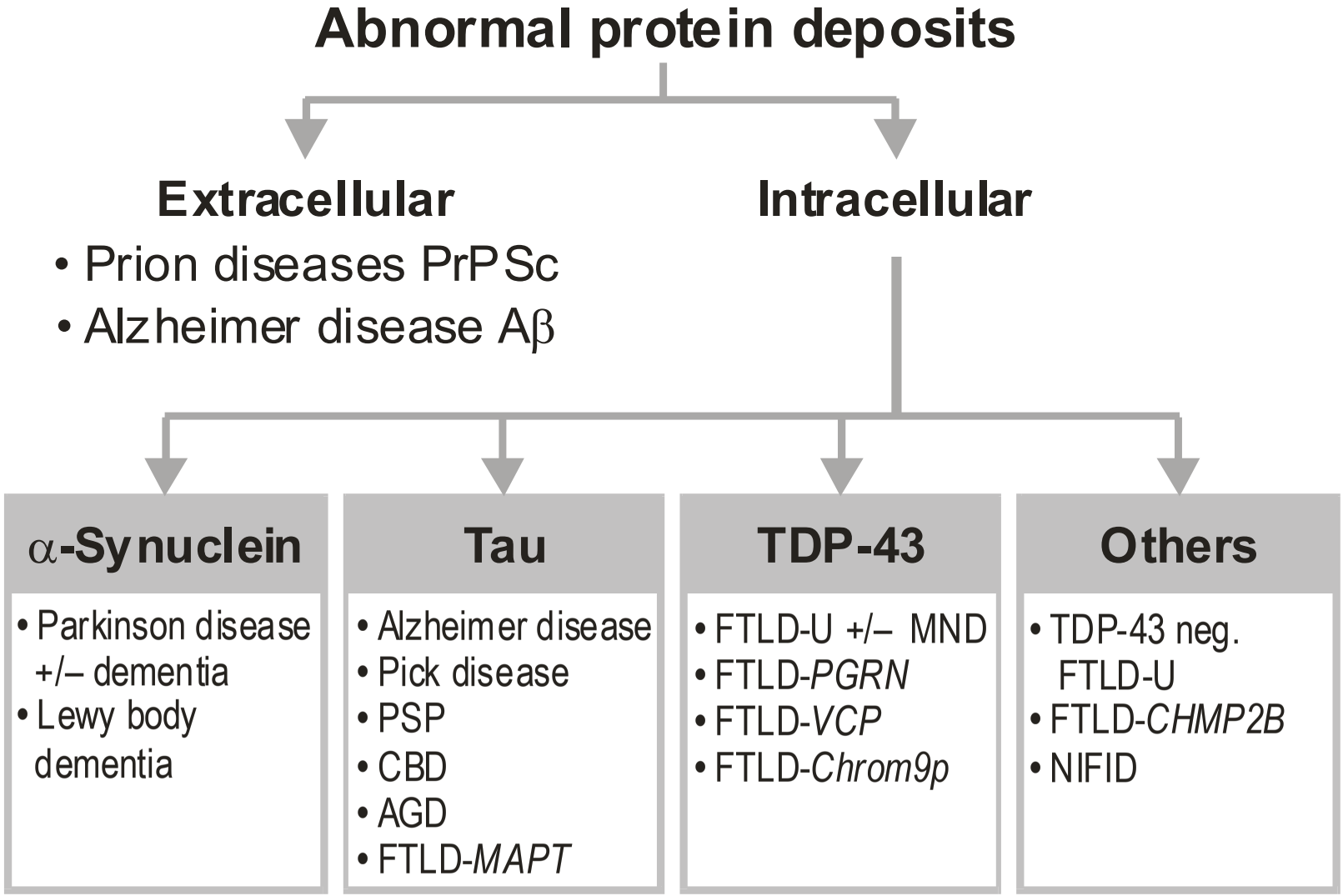
ISBN: 978-960-474-278-3

Table 8. Mixed pathologies frequency in demented elderly

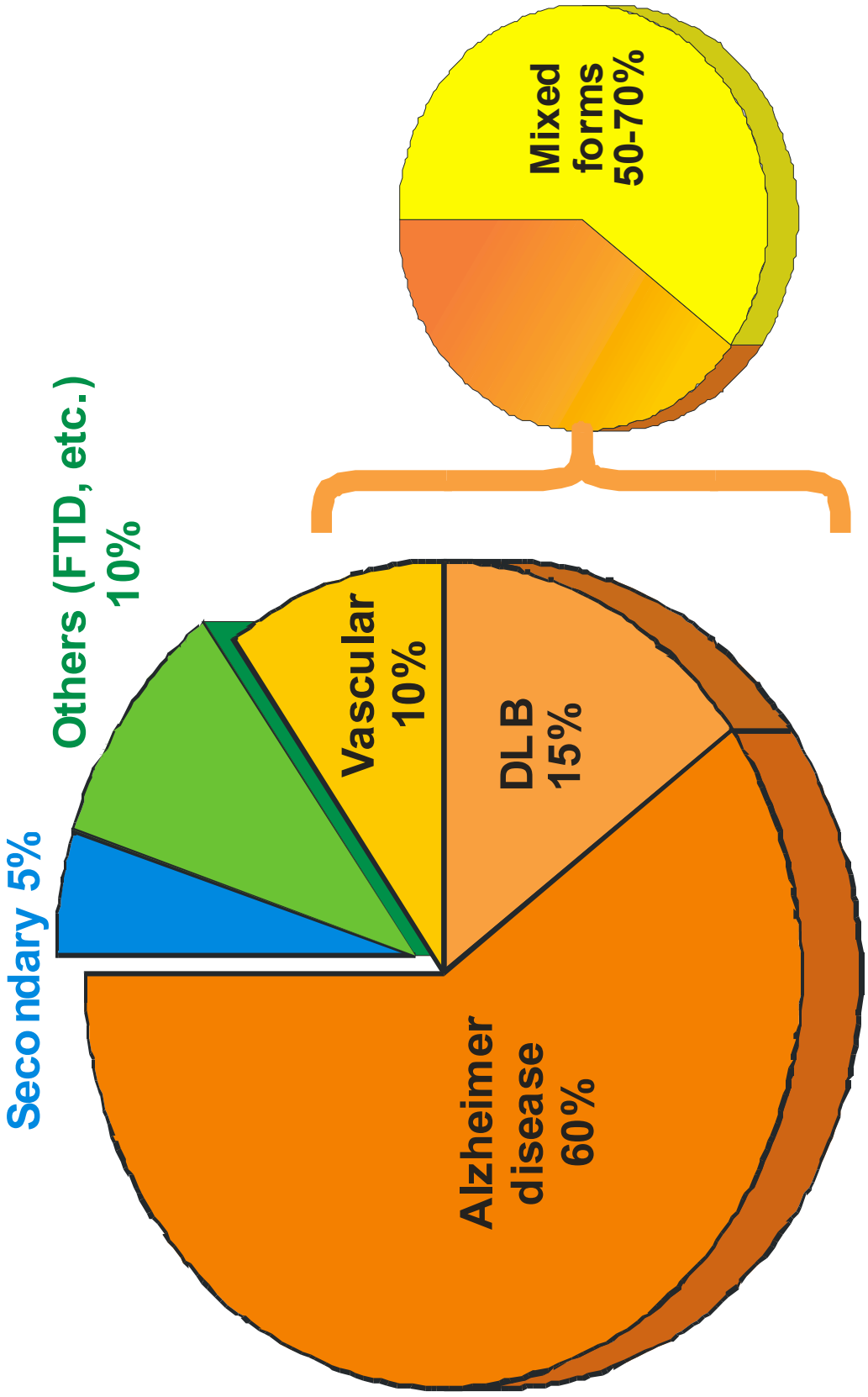
		Pathologies [%]				
Author	**n**	**AD lesions**	**AD alone**	**AD+CVLs**	**AD+LBD**	**VaD**
Nolan et al 1998 [183]	87	87	50	34	–	–
Lim et al 1999 [184]	?	AD cases	36	45	22	–
NUN study - Riley et al 2002 [55]		AD cases	57	73/93	–	–
HAAS study - Petrovitch et al 2005 [54]	333	< 60	36	24	–	24
MRC-CFAS (UK) – Fernando-Ince 2004 [50]	209 (48% dem.)	70	21	–	–	78
Andin et al 2005 [185]	175	–	72 (clin. VaD)	–	28	
Schneider et al 2007 [56]	141	82.7	30	38	12	12
Kovacs et al 2008 (majority other diseases) [53]	3303	25.0	15.3	3.4	3.4	3.6
Jellinger & Attems 2010 [186]	1680 (dem.)	82.4	46.4	24.0	8.5	13.1
Jellinger & Attems (clinical AD, retrospective, unpubl.)	950	93.0	53.2	27.1	9.1	3.0
Jellinger (prospective, unpubl.)	180	76.9	46.8	24.3	15.4	7.7

AD Alzheimer disease, CVL cerebrovascular lesion, LBD Lewy body disease, VaD vascular dementia, unpubl. unpublished, dem. demented, clin. clinical.

ISBN: 978-960-474-278-3



Jellinger Fig. 1



Jellinger Fig. 2

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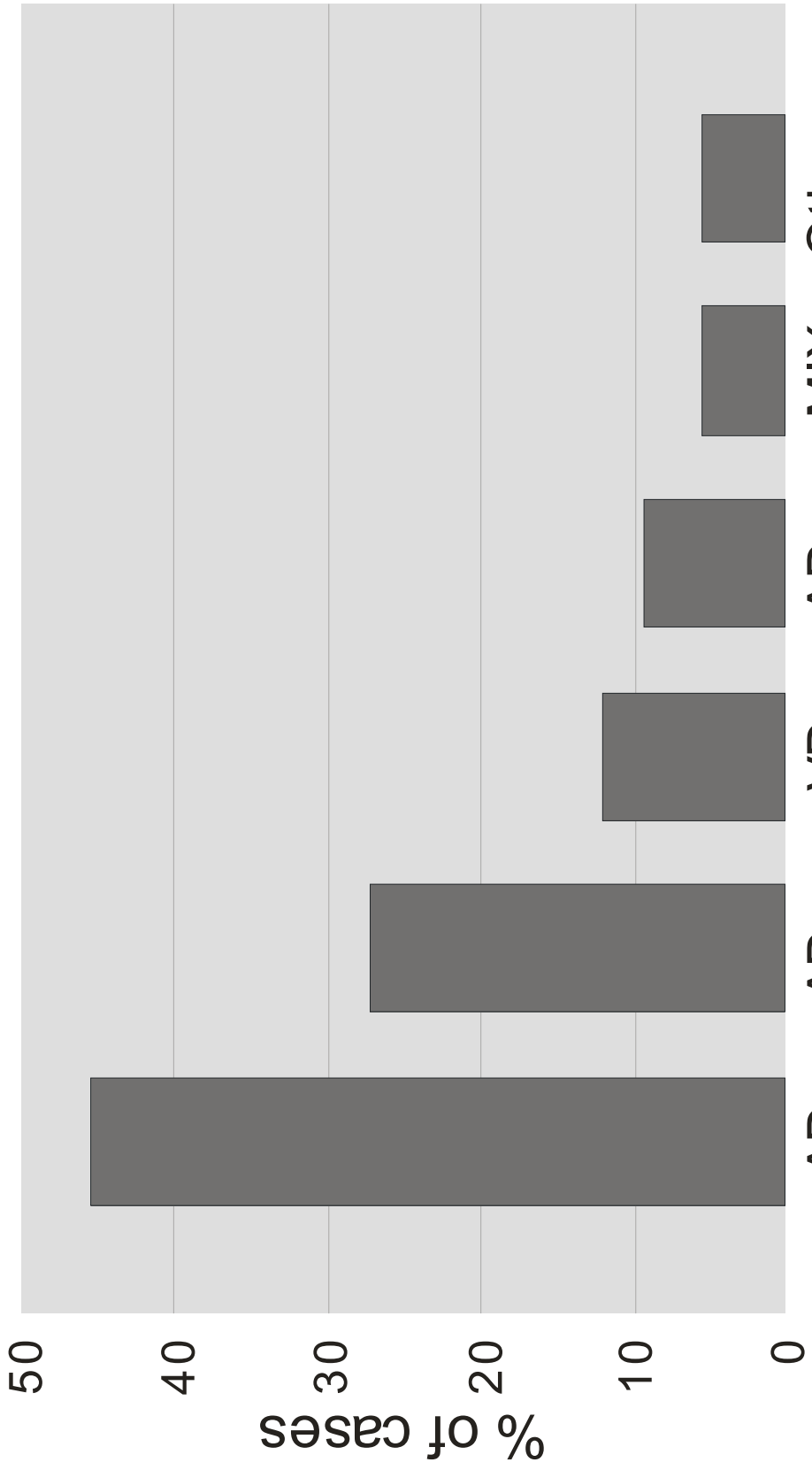

Jellinger Fig. 3

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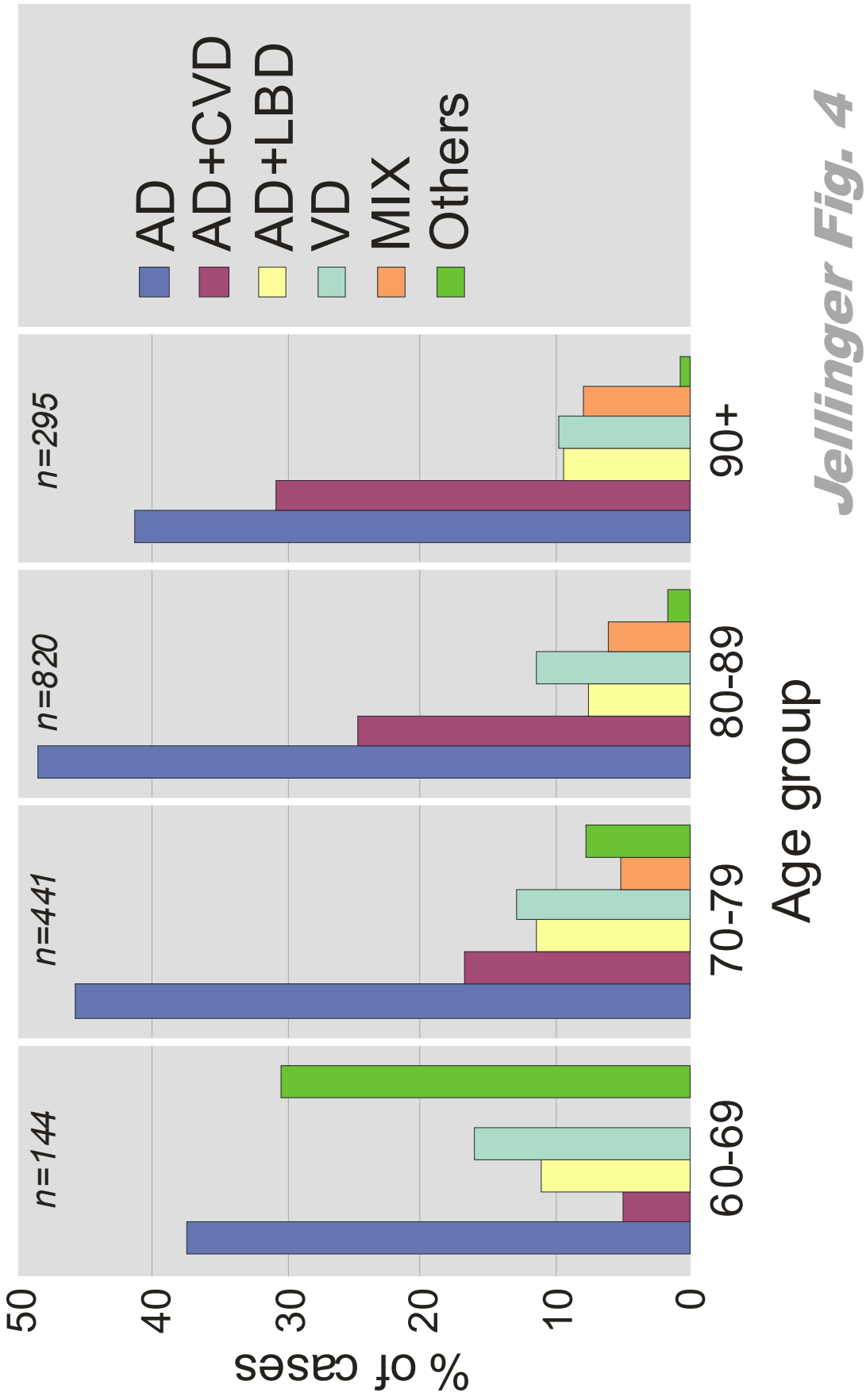

Jellinger Fig. 4

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