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Neuropathology of Dementia Disorders

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Abstract

Dementia, being not a specific disease but a syndrome characterized by deficits in several cognitive domains, is a major public health and socio-economic problem of our century. It is caused by dysfunction/loss of synapses and neurons inducing default neuronal networks. Despite updated concensus criteria for the clinical diagnosis of the major neurodegenerative disorders and new biomarkers, the diagnostic accuracy ranges from 65 to 96% (for Alzheimer's disease /AD), with a sensitivity versus other dementias of around 85.4% and a specificity of up to 77.7%. Pathologic assessment, using genetic and molecular biological methods, based on homogenous definitions, harmonized interlaboratory and assessment standards, can achieve a classification in up to 95%, without, however, clarifying the etiology of most of these disorders. The new National Institute on Aging-Alzheimer Association guidelines ("ABC" score) for the neuropathologic diagnosis of AD combine β-amyloid plaque phases and Braak neurofibrillary scores, also considering other concomitant pathologies, but do not consider distinct clinico-pathologic subtypes of AD. Revised research criteria are available for dementia with Lewy bodies, Parkinson disease-dementia, frontotemporal lobe degeneration, vascular cognitive impairment, prion diseases, and other degenerative dementias. However, due to overlap between proteinopathies, frequent confounding lesions and co-occurence of multiple pathologies in aged brains, human postmortem studies entail biases that affect both their general applicability and validity. Although most degenerative dementias are incurable at present, prospective studies using validated protocols and data fusion may overcome the limitations of the current diagnostic framework as a basis for future personalized therapy options.

Keywords: Dementia, Diagnostic criteria; Neuropathology; Alzheimer's disease; Lewy body disease; Neurodegenerative disorders; Proteinopathies; Prion diseases; Mixed pathologies

Introduction

Dementia, encompassing deficits in several cognitive domains that are severe enough to interfere with daily functioning [1], in the new DSM V classification is classified within the broad category of major neurocognitive disorders, proposing specific criteria for the various etiologies [2]. Previously defined as the manifestation of deteriorating brain functions over time due to cell deaths in the brain caused by neurodegeneration or any other disease [3], according to recent research dementia is not primarily caused by neuronal cell death/loss, but by dysfunction and loss of synapses [4] in AD [5] and in α-synucleinopathies [6]. Other causes include cholinergic neuronal and axonal abnormalities [7,8], as well as pre- and postsynaptic cortical cholinergic deficits also occurring in early AD [9]. These changes due to disconnection of major nervous circuitries causing default networks [10-13] have been demonstrated *in vivo* in early AD [14], suggesting that disease progress is transmitted by neuronal pathways [15]. A prion-like spread of misfolded protein aggregates in the pathogenesis and progression of neurodegeneration is a hot spot of discussion [16-21].

Both the prevalence and incidence of dementia increase exponentially with age. In 2010, 35.6 million people worldwide lived with dementia, with around 8 million new cases every year. Numbers are expected to double or triple every 5-10 years, to 135 millions in 2050, 16 millions in Europe. In 2010, 58% of all demented people lived in low-cost countries, with their proportion anticipated to rise to 71% in 2050 [22]. According to recent data from China the incidence of dementia was 9.87/1000 person years and the median standardised mortality ratio was 1.94:1 [23]. With the disproportional growth of the elderly population, dementia has become a major public health and socio-economic problem that threatens to become the scourge of our century. The total costs for dementia were US$ 604 billion in 2010 worldwide, up to 70% for social care alone [24], total payments for AD for 2013 were expected to be $ 203 billion in USA alone, not included contributions of unpaid caregivers [25].

Clinical Diagnostic Criteria-Diagnostic Challenges

Updated consensus criteria for the clinical diagnosis of the major dementing disorders include: revised NICDS-ADRDA and EFNS criteria for AD [1,26], the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria for AD [27-30], criteria for Parkinson disease-dementia (PDD) [31,32], dementia with Lewy bodies (DLB) [33], frontotemporal lobe degeneration [34,35], vascular cognitive disorder/dementia NINDS-AIREN DSM-IV [36], and other degenerative dementia syndromes [37].

Assessment of clinical data with fusion of different biomarkers has improved the clinical diagnostic accuracy of AD up to 95%. A meta-analysis of 20 (among 1189) records on the accuracy in distingishing AD from other dementia types and healthy controls using autopsy as standard for truth calculated a sensitivity at 85.4% (95% CI 80.9-90.0%) and a specificity at 77.7% (95% C 70.2-85.1%), both values being slightly higher for imaging procedures than for cerebrospinal fluid (CSF) markers. The study also highlights the limited evidence on autopsy-confirmation and heterogeneity of study design [38]. Combination of the best CSF and magnetic resonance imaging (MRI) data using standardized operating measures allows a more precise diagnostic prediction [39,40], and will be further increased by using multimodal techniques and novel CNS biomarkers [41-47]. The validity of plasma biomarkers for the (preclinical) diagnosis of AD and the relation between CSF ApoE levels and cognitive decline have been reviewed

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recently [48,49]. Correlation between CSF biomarkers for AD with amyloid plaques and tau pathology was seen in cortical brain biopsies [50], although there are conflicting results with disease progression and biomarker changes [51-53]. Recent data suggest that both "amyloid first" and "neurodegeneration first" biomarker profile pathways to preclinical AD exist [54]. Although biopsy findings in dementia frequently are non-specific [55], with an overall sensitivity of 65% [56], simulated cerebral biopsies from *postmortem* brains allowed accurate neuropathologic diagnosis in the majority of neurodegenerative diseases [57].

Identification of fibrillar Aβ *in vivo* by $^{(11)C}$PIB PET is feasable for both research and clinical settings [58-61]. Recent evidence comparing amyloid PET studies with postmortem or biopsy results raises doubt about this method as representative of Aβ loads in the living human brain, which may be due to various reasons [62-64]. On the other hand, 55% prevalence of PiB positivity was observed in non-demented subjects aged >80 years, and 85% positivity in the ApoE ε4-positive non-demented elderly subjects [65]. Demonstration that SDS-soluble Aβ measured by immunoassay was better than post mortem PiB binding has important implications for imaging-based biomarkers [66]. In some PiB-negative cases, a combination of pre-existent non-AD pathology and tau-mediated neurodegeneration may be present prior to Aβ pathology [67].

Hippocampal atrophy in the elderly, demonstrated by modern imaging methods and confirmed by postmortem diagnosis of AD [44,68], has been shown to be an important and under-appreciated brain lesion of aging [69].

A review of 2,861 neurodegenerative disease cases of the National Alzheimer's Coordinating Center Registry (NACCR) showed high diagnostic accuracy for AD (85% sensitivity, 51.1% specificity) and low sensitivity for DLB (32% for pure AD and 12% for AD+DLB) with a specificity over 58% [70]. Evaluation of the accuracy of current clinical diagnostic methods for AD in 919 autopsy cases from the database of the NACC (2005-2010) revealed a sensitivity from 70.9 to 87.3% and a specificity of 44.3 to 70.8%. When the clinical diagnosis was not confirmed by minimum levels of AD pathology, the most frequent primary diagnoses were neurofibrillary tangle-predominant dementia (NFTD), argyrophilic grain disease, frontotemporal lobe degeneration (FTLD), cerebrovascular disease (CVD), Lewy body disease, and hippocampal sclerosis. 39% of these cases met or exceeded minimum threshold levels of AD histopathology [71]. In a recent clinico-pathologic restudy of 200 demented brain donors (mean age 78.7 ± 6.9 years, 26% AD, 15.5% mixed dementia, 28% combined diagnoses), the overall agreement between clinical and postmortem diagnoses was 44% (85% for prion disease, 49% for AD), with frequent co-occurrence of multiple pathologies [72]. However, histopathology is still considered to add to *premortem* diagnostic accuracy [71,73,74]. Clinico-pathologic correlations in the most common neurodegenerative dementias have been summarized recently [75].

This review will discuss the diagnostic validity and limitations of current neuropathologic criteria of neurodegenerative dementias, and give recommendations for future clinico-pathologic research.

Updated Pathologic Diagnostic Criteria

Several guidelines for the neuropathologic diagnosis of major dementing disorders are used, relying on qualitative, semiquantitative, and topographic assessment of morphologic and bio/histochemical markers, in particular specific protein inclusions in neurons, glia and other cells [76-79]. The classification of neurodegenerative disorders, previously based on the anatomical systems involved, has been replaced by molecular-pathologic classification (Figure 1), which may provide a basis for their neuropathologic diagnosis in the future [80].

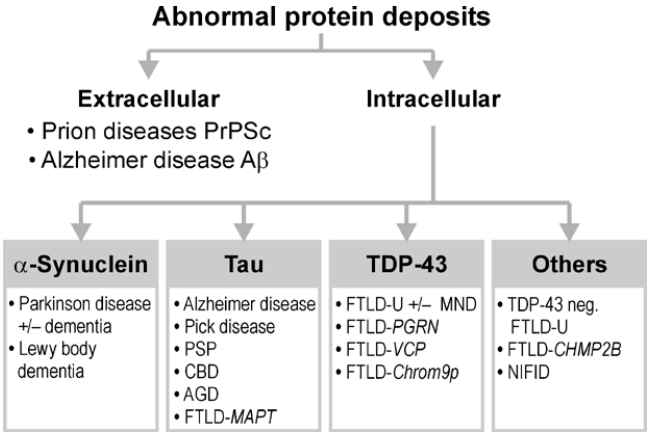

Figure 1: Molecular-pathologic classification of degenerative dementias reproduced with permission from [80].

Alzheimer disease

Neuropathologic criteria for *Alzheimer disease* (AD), include (1) cut-off quantitative values of senile plaques and tangles [81], (2) their semiquantitative assessment and age-adjustment in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) protocol [82], (3) topographic staging of neuritic AD pathology [83], re-evaluated recently [84,85], and the progress and distribution of Aβ deposition being different from tau pathology [86].

Standard metrics for tangles and neuritic plaques are usually semi-quantitative and, according to the Brain Net Europe consortium, good agreement can be reached in the diagnosis only when the lesions are substantial, having reached isocortical structures (Braak stage V-VI with absolute agreement 91%), while for mild lesions the agreement was poorer (Braak stage I-II, agreement 50%) [84], thereby limiting the ability to make accurate correlation of *antemortem* cognitive status and morphologic findings [87]. Furthermore, multiple concomitant brain damage contributes to the uncertainty of AD clinicopathologic correlations based only on plaques and tangles [88].

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 [89]. These diagnostic categories apply only to demented individuals. Evaluation of the NIA-RI critera demonstrated their easy 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 [90].

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 [80]. Thus, their predictive value may be reduced to 38-44% [91]. 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 (ABC 3/3/3) without other pathologies in only 41.0%, AD with concomitant pathologies including mixed dementia in 44.8%, vascular dementia in 10.7%, other disorders in 5.5%, and negative pathology in 0.9% [87,90]. Although cognitively normal elderlies may show variable neocortical AD-related pathology, in general, the number of isocortical tangles correlates best with the severity of cognitive impairment [92-94]. The pattern of gray matter loss associated with tangle pathology is an appropriate *in vivo* surrogate indicator of AD pathology [95]. The predictive value of widespread tau pathology (Braak stages V-VI) for dementia is high [93,94], 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 [96]. A recent study found that the amyloid stage that has progressed to involve the striatum is highly predictive of dementia [97]. The cortical Aβ burden usually does not correlate with disease duration and the stage of tau pathology [98].

The recently revised guidelines for the neuropathologic evaluation of AD and other diseases consider levels of AD pathology in the brain regardless of the clinical status of a given individual [99,100]. They include (1) recognition that AD neuropathology may occur in the apparent absence of cognitive impairment, (2) an "ABC" score of AD neuropathologic changes that incorporates histological assessments of Aβ deposits (A), based on the phase assessment of amyloid [86], staging of neurofibrillary tangles/NFT) (B), based on the Braak staging system, and scoring of neuritic plaques, based on semiquantiative assessment in at least five neocortical regions (C), based on CERAD criteria [82] (Table 1), (3) more detailed approaches for assessing co-morbid conditions, such as LB disease, vascular brain injury, hippocampal sclerosis, and TAR DNA binding protein (TDP-43) immunoreactive lesions [100]. Correlations between neuropathologic AD changes with cognitive status were reviewed recently [94]. Testing the revised NIA-AA guidelines for the assessment of AD in 390 autopsy cases (including 199 non-demented individuals) distinguished pure AD and non-AD dementia from non-demented cases with a sensitivity of 71% and a specificity of 99%. The sensitivity increased after neuropathologic exclusion of non-AD dementia cases, indicating that cognitive status and assessment according to NIA-AA guidelines appear ideal for distinguishing pure AD from non-AD dementia, preclinical AD and nondemented controls [101].

		Levels of AD neuropathologic changes				
"A"	Thal Phase for Aβ plaques	"B"	Braak and Braak NFT stage		"C"	CERAD score
0	0	0	None		0	None (neg.)
1	1 or 2	1	I	or II	1	Sparse (A)
2	3	2	III	or IV	2	Moderate (B)
3	4 or 5	3	V	or VI	3	Frequent (C)

AD neuropathologic change		B		
A	C	0 or 1	2	3
0	0	Not[a]	Not[a]	Not[a]
1	0 or 1	Low	Low	Low[b]
	2 or 3[f]	Low	Intermediate	Intermediate[e]
2	Any C	Low[c]	Intermediate	Intermediate[e]
3	0 or 1	Low[c]	Intermediate	Intermediate[e]
	2 or 3	Low[c]	Intermediate	High

[a] High levels of neuritic plaques and low Thal Aβ phase are rare and should prompt reconsideration

[b] Widespread NFTs with some Aβ plaques but limited neuritic plaques are infrequent

[c] High levels of Aβ or neuritic plaques with low Braak stage should prompt consideration of co-morbidity, eg, CVLs, etc.

Table 1: "ABC" score for AD neuropathological changes. Modified with premission from [100].

Problems in the neuropathologic diagnosis of Alzheimer's disease

Histopathologic examination of the brain establishes that AD-related lesions are present in sufficient densities to distinguish AD from age-related lesions and other dementing disorders [99,100,102]. The current algorithms for the neuropathologic diagnosis of AD are based on (semiquantitative) assessment of plaques and tangles. Despite reasonable interrater agreement when using standardized criteria [84,103-105], no one set of histopathologic criteria for AD has been uniformely accepted by neuropathologists. These algorithms that only considered the classical "plaque and tangle" phenotype of AD did not recognize other subtypes [74,106,107]. Analysis of 1,677 cases with *antemortem* diagnosis of dementia from the NACCR showed that 82.4% fell into diagnostic "boxes" that are within the consensus recommendations, while the others were "atypical" cases [108]. Posterior cortical atrophy, a clinico-radiologic syndrome considered an atypical variant of AD [109] morphologically shows greater NFT burden in the occipital and parietal lobes and lower in hippocampus [110], while we recently published a 4-repeat tauopathy clinically presenting as posterior cortical atrophy of long duration [111].

The "*plaque predominant*" type with abundant amyloid plaques, no or very little neuritic pathology restricted to the hippocampus and abnormal phosphorylated tau in neocortical pyramidal cells but lacking overt tangle formation, accounts for 3.5-8% of demented subjects over age 85 [112,113]. Many of them are associated with cortical LBs representing a specific type of DLB or LB variant of AD (LBV/AD) [114]. The "*neurofibrillary tangle predominant dementia*" (NFTD) with tau pathology often restricted to the limbic system, absence of neuritic plaques, no or very little (diffuse) amyloid plaques and rare amyloid angiopathy accounts for 5-7% of oldest olds with low ApoE ε4 frequency. Recent molecular and genetic analysis confirmed an identical tau isoform composition in TPD and AD [115], and demonstrated absence of soluble Aβ but elevated soluble amyloid precursor protein α (APPα) in brain tissue, and association with the tau gene MAPT H1 haplotype, classifying it as a specific tauopathy independent of amyloid [116].

A recent study of autopsy-proven AD cases separated distinct subtypes: (a) hippocampal-sparing AD (HpSp-AD) with lower NFT counts in hippocampus but more frequent senile plaques compared to typical AD (11%), (b) limbic-predominant forms (LP-AD) with lower cortical NFT counts and tau burden (14%), and (c) typical AD (75%). AD subtypes havd pathologic, demographic, clinical, and genetic differences [117]. HpSP-AD cases were younger at death, while the disease duration in all three types was similar. Additional vascular pathology ranged from 16 to 36%, and Lewy pathology (11-26%) was lowest in HpSP-AD. While MAPT H1H1 genotype was high (~70 %) in NFTD and LP-AD, and similar to typical AD (59%), tau and Aβ burden in frontal cortex were very low in NFTD, differentiating it from AD subtypes, including LP-AD. Significant pathological differences between NFTD and LP-AD suggest that it may not merely be a variant of AD [106]. Volumetric MRI analysis could reliably track the distribution of NFT pathology and predict pathological subtypes of AD [118]. Hippocampal sclerosis of aging showing neuronal loss and gliosis out of proportion of AD-type pathology is a prevalent and high-morbidity brain disease [69,119].

Among 933 autopsy-confirmed AD cases, typical AD accounted for 82.5%, HsSP-AD and LP-AD 8.2 and 8.9%, respectively. Disease

duration was lowest in LP-AD cases; age at death highest in typical AD. Additional cerebrovascular pathology was similar in all three types, Lewy pathology most frequent in HpSP-AD form [107] (Table 2). These two studies and one from the NACCR, separating "tangle intensive" and "plaque intensive" cases from classic AD [108] emphasize the need for prospective clinico-pathological studies for further elucidation of various phenotypes of AD.

In addition, considerable phenotypical and morphological differences exist between genetic/familial and sporadic AD [120-123]. In a recent autopsy study, upstream transcription factor 1 (USF1) carriers had lower tangle prevalence among 65+ year olds [124].

Another problem is the relationship between subcortical tau pathology and AD. The stepwise progression of tau pathology in aging and AD is generally assumed to begin in the entorhinal cortex, progressing via the hippocampus to neocortical regions [83]. However, recent studies indicate that tau pathology does not initially manifest in mediotemporal cortex but in selected subcortical nuclei, in particular the locus ceruleus that is suggested to have a distinctive role in the early development of sporadic AD [125,126]. Examination of 239 unselected elderly autopsy cases already in Braak stage 0 showed very sparse (pretangle) tau lesions in 53% in the olfactory bulb and in 44% in locus ceruleus, with increasing prevalence and severity of tau pathology in these nuclei with increasing Braak stages, suggesting that they are increasingly involved during AD progression rather than representing sites initially affected by AD-associated tau pathology [127,128].

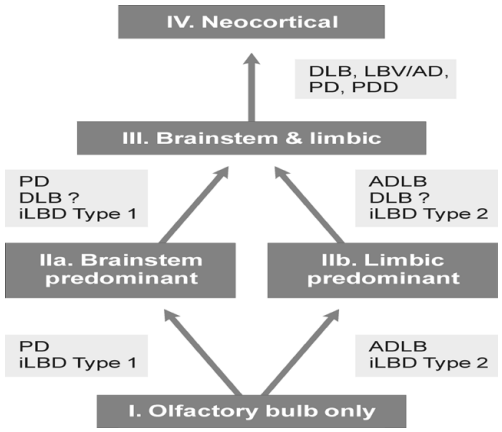

Figure 2: Scheme of the progression pathways and stages of Lewy body (LB) disorders. The pathway for Parkinson's disease (PD) is suggested to proceed through stage IIa (brain stem predominant) and that for dementia with Lewy bodies (DLB) and Alzheimer's disease (AD) with LBs probably pass through stage IIb. For incidental LB disease (iLBD), both pathways seem possible, whereas only PD/PD dementia (PDD), DLB, and the LB variant of AD (LBV/AD) progress to the neocortical stage. Modified with permission from [142].

Further studies are warranted to elucidate whether tau pathology in the locus ceruleus of young individuals is associated with AD or rather reflects non-specific neuronal damage.

Diagnostic criteria for other dementias

α-Synucleinopathies, in particular Lewy body disorders - Parkinson's disease (PD) and dementia with Lewy bodies (DLB) -, a frequent type of dementia in the aged, show a multiorgan distribution of phosporylated αSyn, with earliest involvement of the gastrointestinal tract and olfactory bulb [129-132]. Staging/classification systems based on the semiquantitative assessment of the progression pattern of αSyn pathology [33,133] are suggested to indicate a predictable sequence of lesions [130,131]. Clinico-pathologic studies, although partly confirming this grading system [134], revealed that between 6.3 and 47% of autopsy-proven PD cases did not follow the proposed caudo-rostral spread of Lewy pathology [132,135-138]. In 7-8.3% of PD cases, the dorsal motor nucleus of vagus was not involved despite definite αSyn inclusions in the higher brainstem or even in cortical regions [137-139]. On the other hand, 30-55% of elderly subjects with widespread/cortical αSyn pathology had no neuropsychiatric symptoms or were not classifiable [139-141]. Therefore, the criteria for categorization of Lewy-related pathology have been modified (Figure 2). It should be emphasized that Lewy bodies (LB) occur early in the olfactory bulb and usually are present outside of the brain in the autonomic and peripheral system and in many organs [142,143].

PD-dementia (PDD) and DLB, sharing many clinical and morphologic features, are believed to form a continuum within the spectrum of LB diseases [33,144]. Clinically, an arbitrary cut-off is used: if dementia develops first or within one year of PD diagnosis, then DLB is diagnosed, while dementia developing more than one year after PD motor symptoms suggests PD-dementia. The pathologic hallmarks of both phenotypes are αSyn/LB pathology or a variable mixture of LB and AD pathologies, which may act synergistically [145]. The severity and extent of αSyn are scored semiquantitatively in specific brain regions [33,133]. DLB differs from PD-dementia by more severe diffuse amyloid load in the striatum [146,147], more frequent LB affection of the hippocampal CA 2-3 subareas [132], but lack of pedunculopontine cholinergic cell loss that was significant in PD with hallucinations, indicating different patterns of degenerations of cholinergic output structures in PD and DLB [148]. DLB cases had more severe Aβ load than PD-dementia; but no differences in neuritic and αSyn scores, while others reported higher Aβ load in cortical and subcortical areas [145,149], the Aβ load being similar to that in AD [150,151]. Between 10 and 50% of PD-dementia brains had enough AD-like lesions to attain the pathological diagnosis of definite AD [152], but cognitive impairment may also be related to higher Braak LB stages in the absence of significant AD pathology [153]. According to a recent clinico-pathologic study cortical LB/LN pathology is the most

Characteristics	Hippocampal-sparing AD (n = 79, 8.2%)	Limbic-predom. AD (n = 85, 8.9%)	Typical AD (n = 769, 82.5%)	P value
Women	59.5%	64.7%*	67.5%*	* versus HS P < 0.01
Age at death	76.3 ± 8.6	84.9 ± 3.8*	81.3 ± 9.2*	* versus HS P < 0.01
Age at onset	68.0 ± 10.0	73.8 ± 6.4*	79.7 ± 3.8*	P < 0.01; * versus HS <0.001
Disease duration	7.4 ± 3.6**	4.8 ± 2.6***	9.1 ± 4.3*	***P < 0.001; ** versus HS P < 0.001
MMSE final (mean)	10 (n = 20)	11.5 (n = 16)	4.6 (n = 78)*	* versus other forms P < 0.01
Braak NFT stage (mean)	4.5 (2–5)	4.5 (3–5)	5.6 (5–6)	
Cerebrovascular pathology	34.2% *	41.1%	36.4% *	* versus. LP P < 0.01
Lewy body pathology	24.9% *	3.5%	8.2%	* versus. other forms P < 0.001

Table 2. Major characteristics of AD subtypes. Reproduced with permission from [107].

significant correlate of dementia in PD, while AD pathology, being abundant in a subset of patients, may modify the clinical phenotype [154]. On the other hand, up to 50% of AD cases exhibit additional LB pathology, which is associated with a more aggressive disease course and accelerated cognitive dysfunction [155].

Frontotemporal lobe degeneration (FTLD), the third most frequent cause of dementias, with an estimated prevalence of 15-22/100.000 people aged 46 to 64 years [156] includes three major clinical subgroups: behavior variant (bvFTD), semantic dementia (SD), and progressive non-fluent aphasia (PNFA), showing distinct patterns of progressive brain atrophy [157]. The most common of their molecular correlates according to the predominant protein aggregates are: microtubulus-associated tau protein (FTLD-tau), TAR-DNA binding protein-43 (FTLD-TDP-43), and fusion sarcoma protein (FTLD-FUS), but there are cases with overlapping pathology [35,158-160]. Criteria for their neuropathologic diagnosis based on biochemical markers are summarized in Figure 3. Up to 40% of FTD patients have a familial background, and 30-50% of familial cases show autosomal-dominant traits; furthermore, various gene mutations have been described [159]. The three major genetic causes of FTLD are mutations in MAPT, progranulin (GRN) and C9orf72. The clinical and pathological phenotypes of FTLD with C9orf72 mutations have been reviewed recently [161]. An expanded GGGGCC repeat in a non-coding region of the C9orf72 gene is a common cause of FTLD and amyotrophic lateral sclerosis (ALS) [162]. FTLD in elderly patients presents features of several phenotypes and morphologic

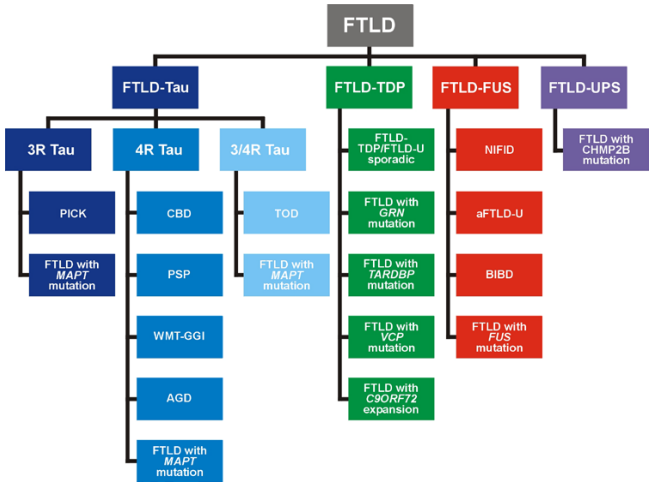

Figure 3. The molecular and genetic classification of frontotemporal lobe degeneration. Three distinct neuropathologic categories may be identified based on the molecular pathology of the misfolded protein within the inclusion: FTLD-Tau, FTLD-TDP, and FTLD-FUS; the molecular pathology of a fourth category, FTLD with epitopes of the ubiquitin–proteasome system (FTLD-UPS), remains indeterminate. 3R, 4R, 3R/4R the predominant tau isoform within the inclusion; PICK, Pick's disease; FTLD with microtubule-associated protein tau (MAPT) mutation with inclusions of 3R, 4R, or 3R and 4R tau protein; CBD, corticobasal degeneration; PSP, progressive supranuclear palsy; AGD, argyrophilic grain disease; TOD, tangle only dementia; WMT-GGI, white matter tauopathy with globular glial inclusions; FTLD-U, FTLD with ubiquitin inclusions, now called FTLD-TDP; FTLD with progranulin (GRN) mutation; FTLD with TAR DNA-binding protein 43 (TARDBP) gene mutation; FTLD with valosin-containing protein (VCP) mutation; FTLD with C9ORF72 expansion, chromosome 9-linked FTLD with C9ORF72 hexanucleotide repeat expansion; NIFID neuronal intermediate filament inclusion disease; aFTLD-U atypical FTLD with ubiquitin inclusions; BIBD basophilic inclusion body disease; FTLD with fused in sarcoma (FUS) mutation; FTLD with charged multivesicular body protein 2B (CHMP2B) mutation. There may still be unclassified entities within each molecular pathology grouping. Reproduced with permission from [160].

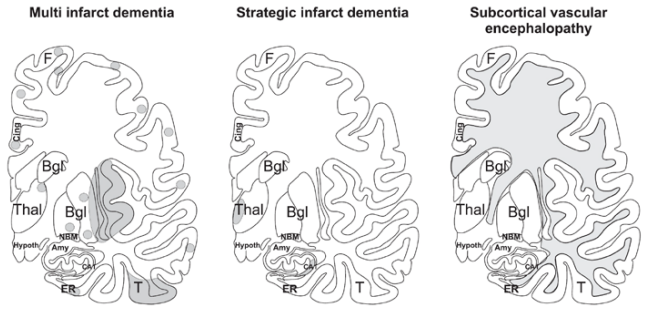

Figure 4. Schematic representation of multi infarct dementia, strategic infarct dementia, and subcortical vascular encephalopathy. The gray areas mark the regions where infarcts and white matter lesions are located. In multi infarct dementia multiple microinfarcts, lacunar infarcts, and small large infarcts are distributed all over the gray matter. Strategic infarct dementia is characterized by infarcts in strategic regions that alone explain dementia, i.e., in the hippocampal formation and in the paramedian nuclei of the thalamus. Subcortical vascular encephalopathy is characterized by confluent white matter lesions in the central and peripheral white matter. Small infarcts in subcortical brain regions may also co-occur with this type of VaD. Amy=amygdala, Bgl=basal ganglia, CA1=Ammon's horn sector CA1, Cing=cingulate gyrus, ER=entorhinal cortex, F=frontal neocortex, Hypoth=hypothalamus, NBM=basal nucleus of Meynert, T=temporal neocortex, Thal=thalamus. Reproduced with permission from [182].

subgroups similar to that seen in the presenile group, though patients with MAPT (tau-gene), but not GRN mutations or FUS pathology are rare or even absent [163]. However, these authors found significantly more frequent hippocampal sclerosis but milder frontal atrophy in the elder group [164], which was confirmed in two cases of FTLD tau aged 85 and 88 years, respectively [165]. Inclusions in FTLD-TDP and ALS but not in FTLD-FUS have properties of amyoid [166]. TDP-43 positive inclusions are also observed in cases with AD and LB pathologies [167], and cognitively normal individuals [168], while FUS-immunoreactive intranuclear inclusions occur in various neurodegenerative diseases [169], but it is not clear whether these changes are a primary, secondary or coincidental event [170].

V*ascular dementias* (VaD) or vascular cognitive impairment (VCI) (related to CVD, or more recently vascular cognitive disease), are suggested in 8-15% of demented patients; their prevalence in autopsy series varies from 0.03 to 58% (with means of 8 to 15%). Clinical diagnostic criteria show moderate sensitivity (around 50%) and variable specificity (range 64-98%) [171]. Despite several proposals for a categorization of major cerebrovascular lesions (CVLs) [172-176], a harmonization of the criteria and techniques for the assessment of cerebral lesions of presumable/possible vascular origin in cognitively impaired is necessary [177,178]. Due to the high variability of morphologic findings and multifactorial pathogenesis of vascular cognitive impairment, no generally accepted morphologic scheme for quantitating cerebrovascular lesions and no validated neuropathologic criteria for VaD have been established to date [172,175,179]. The revised NIA-AA guidelines recommend reporting all macroscopic and microscopic CVLs, multiple such lesions being associated with increased likelihood of cognitive impairment [100]. Major types of CVLs are multiple infarct encephalopathy, small vessel and strategic infarct type dementia (microinfarcts in functionally important brain areas interrupting major neuronal circuitries), subcortical lacunes, white matter lesions and microinfarcts (subcortical arteriosclerotic /leuko/ encephalopathy Binswanger) [172,180-182] (Figure 4). A recent staging strategy proposing semiquantitative assessment of CVLs in 4 brain areas with a score from I to IV/VI [183] (Table 3) needs further evaluation.

Score	Staging
Frontal and temporal lobes	
0	Normal appearance of brain, vessels, white matter, and cortex
I	Mild modification of vessel walls, perivascular spaces, or white matter
II	Moderate to severe but isolated modification of the vessel walls (arteriolosclerosis or amyloid angiopathy), usually associated with hemosiderin deposits in the perivascular spaces
III	Moderate to severe perivascular space dilatations either in the deep or the juxtacortical white matter
IV	Moderate to severe myelin loss
V	Presence of cortical microinfarcts
VI	Presence of large infarcts
Hippocampus	
0	Normal appearance
I	Mild modification of vessel walls or perivascular spaces
II	Moderate to severe perivascular space dilatations
III	Presence of microinfarcts (usually in Ammon horn or the subiculum)
IV	Presence of large infarcts
Basal ganglia	
0	Normal appearance
I	Mild modification of vessel walls or perivascular spaces
II	Moderate to severe perivascular space dilatations
III	Presence of microinfarcts
IV	Presence of large infarcts
Total vascular score	Frontal + temporal lobe + hippocampus + basal ganglia (/20)

Table 3. Staging of the cerebrovascular lesions. Reproduced with permission from [183].

Mixed type dementia, occurring in 25 to 80% of elderly demented persons, is diagnosed when a combination of several pathologies, e.g. AD with cerebrovascular lesions and/or Lewy pathology, is present [184-187]. CVD and vascular brain injury commonly are encountered in the brains of seniors with and without AD pathology [175,180,184,185], but uniform and reproducible criteria are currently not available. Subcortical CVLs were more frequent in AD patients than in non-demented controls and more frequent in severely demented patients with early onset AD [188].

Prion diseases (transmissible spongiform encephalopathies/TSE) are rare fatal neurodegenerative disorders, with tissue deposition of a misfolded isoform of the cellular prion protein (PrP), referred to as PrP^{Sc} [189]. They are classified by both clinicopathologic syndromes and etiology with subclassification according to molecular criteria [190,191]. Human prion diseases are grouped into three etiologic categories [192,193]: (1) Idiopathic forms: sporadic Creutzfeldt-Jakob disease (sCJD) - age at onset 50-78 (mean 60) years, mean duration 5 months, sporadic familial insomnia (sFI), and the recently described variably protease-sensitive prionopathy [194]; (2) inherited (genetic or familial) forms such as Gerstmann-Sträussler-Scheinker disease (GSS), fatal familial insomnia (FFI), octapeptide repeat insert [195,196], rare familial prion disease with AD-like tau pathology [197], genetic CJD associated with the E200K mutation [198], and (3) acquired forms, such as iatrogenic CJD (iCJD), Kuru, and variant CJD (vCJD) (transmission of bovine spongiform encephalopathy/BSE/ to humans) – age at onset 12-74 (mean 27) years, mean duration 14 months [199]. More than 80% of human prion diseases manifest as sCJD with an incidence of 1-2 cases/million population/year across the world. Around 15% are associated with autosomal dominant pathogenic mutations of the PRNP gene located on the short arm of chromosome 20. To date, more than 37 pathogenic mutations and 29 non-coding polymorphisms have been described. Acquired human prion diseases are rare (only 5% of human prion diseases): transmission of sCJD prions occurred through treatment with pituitary hormones pooled from human cadavers, transplantation of dura mater or cornea, use of contaminated EEG electrodes, and by cannibalism among the Fore linguistic group in Papua New Guinea [200]. vCJD occurred mainly in the UK and in other countries due to human exposure to BSE prions, and more recently in a few cases by transmission of vCJD contaminated blood products [201].

Given the biological and phenotypic heterogeneity of prion diseases, the correct identification or "typing" of the prion strains associated with each case of human TSE has implications for diagnosis, epidemiologic surveillance, and future therapeutics. Either molecular or histopathologic data (or both) may, therefore, provided reliable surrogate markers for strains typing in humans. The current classification of sporadic human prion diseases recognized six major phenotypic subtypes with distinctive clinicopathologic features, which largely correlated at the molecular level with the genotype at the polymeric codon 129 (methionine, M, or valine, V) in the prion protein gene and with the size of the protease-resistent core of the PrP^{Sc}. Six different strains of prions according to the 129 PrP genotype have been distinguished showing differerent frequences, age at onset, duration, clinical and morphologic phenotypes. In addition, about 6% are mixed cases [192].

Based on this and other, slightly different definitions [194,202] and on the distribution and severity of histopathologic lesions, a general nomenclature for the diagnosis of sCJD in the absence of molecular data was proposed relating the histopathology lesion (type, location and distributon of PrP deposits and plaques) with molecular types (MM, MV, VV, etc.) [203]). According to a recent inter-rater study among surveillance centers in Europe and USA, the use of this consensus classification of human TSE histotypes allows reliable identification of molecular subtypes with full agreement for the two most common sCJD subtypes and vCJD, with high concordance for all pure phenotypes and the most common subtypes with mixed phenotypic features [203]. The current classification of human prion disease indicates that, besides molecular PrP^{Sc} typing, histopathologic analysis permits reliable disease classification with high inter-laboratory accuracy.

Rapidly Progressive and Early Onset Dementias

In contrast to most dementing conditions that typically develop over years, rapidly progressive dementia (RPD) being quickly fatal is an important challenging problem. The differential diagnosis shows a wide range, and in addition to frequent prion diseases includes rapidly progressing neurodegenerative tauopathies and synucleinopathies, autoimmune condition infections, toxic-metabolic and neoplastic diseases [204-206]. According to the US National Prion Disease Pathology Surveillance Center (NPDPSC) in patients with RPD, treatable disorders are frequently mistaken for CJD [207]. A rapidly progressive dementia with thalamic degeneration and cortical prion immunoreactivity but absence of resistent PrP has been reported recently [208].

Among 1,106 brain autopsies of RPD, 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 [207]. In a rapidly progressing form of AD that clinically may mimic CJD, the genetic profile (absence of ApoE ε4 homozygenity and biomarkers) differs from classical AD, suggesting that it might represent a distinct subtype of AD [209].

The diagnosis of young-onset dementia, showing a highly variable epidemiology [210], presents challenges that differ from those of older patient frequently driven by the identification of genetic mutations causing early-onset familial disease [211]. However, despite absence of absolute concordance between clinical phenotype and underlying pathology, they can be distinguished with high accuracy. Among 228 cases with early-onset dementia, 46% were diagnosed with AD and the remaining cases DLB, CJD, VaD, or unclassified dementia. AD was identified with 97% sensitivity and 100% specificity, FTLD with 100% sensitivity and 97% specificity [212]. Non-degenerative non-vascular cases of dementia being more common than expected in patients with a younger onset (30% of younger-onset and 5% of older-onset group aged 70-99 years) include cancer, chronic alcoholism, chronic mental illness, and others [213]. The problem of young-onset dementia was reviewed recently [214].

Neuropathology in Nondemented Elderly Subjects and Pre-Alzheimer Disease

The presence of AD lesions in non-demented aged people may represent AD at a stage prior to clinical expression (presymptomatic, preclinical state) [215-219]. The mechanisms responsible for these changes in non-demented elderly appear similar if not identical to those found in AD [218,220]. The concept of "preclinical AD" pathology has been solidified by *in vivo* PET scanning, suggesting its high frequency in normal elderly similar to that seen in clinico-pathologic cohorts [42,61,221,222]. These data further suggest that preclinical stages are not static but progressive over time [58,223].

Preclinical AD, in clinical terms, includes all AD biomarker-positive (CSF tau, Aβ, amyloid imaging) non-demented subjects [224-226] and is associated with future cognitive decline and mortality [227]. According to the neuropathologic definition it includes all non-demented cases with NIA-AA AD pathology. Dissociating clinical symptoms from pathologic findings better allows for investigation of preclinical AD. Although the severity of the pathology, particularly neurofibrillary tangles, has a large role in determining the extent of symptoms, other factors, including age, ApoE status, and comorbidities such as CVD also explain differences in clinical presentation [228].

In non-demented individuals, amyloid and neuritic plaques are usually accompanied by usually mild tangle scores (corresponding to Braak tau stages 0-IV, with a mean ranging from 1.2 to 2.3) and are considered to represent asymptomatic or preclinical AD [101,228,229]. Others reported considerable AD-related pathologies in cognitively intact seniors [216,219,230-232]. However, in the majority of older persons without cognitive impairment, AD-related lesions do not represent the single lesions but are frequently associated with CVD, cortical LBs, and other concomitant pathologies [229,233-237]. A recent comparison between AD, pre-AD and non-AD cases, classified according to current criteria, using neuropathology and detection of soluble, high-molecular-weight Aβ aggregates in a large autopsy series showed elevated Aβ in clinical AD compared to pre-AD and non-AD cases. This suggests that, in addition to more widespread AD-related pathologies, soluble Aβ aggregates in the neuropil play a role in the conversion of Pre-AD to clinical AD. In addition, detection of NFTs, cerebral amyloid angiopathy (CAA) and granulovacuolar degeneration in the absence of amyloid plaques suggests that these lesions may precede Aβ deposition and may represent a pre-amyloid stage of pre-AD not yet considered in current recommendations for the neuropathological diagnosis of AD [101].

Review of the data from National Disease Coordinating Center (NDCC) database and the NUN study emphasized that there may be no documented examples of truly endstage fibrillary pathology with intact cognition [238]. Although in the Adult Changes in Thought (ACT) and NUN studies, non-demented seniors with severe AD pathology (mean age 89 to 91 years) amounted to 8 and 12%, respectively, most of them showed neuritic Braak stage V and frontal NFT count was slightly lower than in a comparable dementia group [231]. However, most of the individuals classified as non-demented in those studies were indeed memory-impaired [231,239]. There is obviously no reported case of truly intact cognition despite severe AD pathology, ie., seniors with widespread neocortical NFTs [94]. Among non-demented elderly 62% demonstrated low and 28% high NFT levels [240], whereas AD cases showed much higher cortical neuritic and striatal amyloid plaque scores [97]. A 90+ study revealed significantly less severe Aβ, αSyn and TP'D-43 pathologies and hippocampal lesions in non-demented subjects, while Aβ distribution showed no essential differences; non-demented individuals had limited hippocampal tau and neocortical Aβ pathology [241]. On the other hand, NFTs in the occipital cortex of 24% of non-demented subjects aged 42-87 years were reported [242].

Thus, mounting evidence supports the view that AD is a continuous spectrum between asymptomatic lesions in cognitively unimpaired seniors and dementia, with mild cognitive impairment (MCI) as a transition between them [243]. Although correlations between cognitive deficits and the severity and extension of plaques and tangles have been found [94], at least in those brains without other pathologies, the distinction between "physiological" (in non-demented subjects) and "pathological" aging (PA) may be difficult. Recent biochemical studies found excessive overlap with only subtle quantitative differences between amyloid levels, peptide profiles, solubility, and oligomeric assemblies in PA and AD brains [244], suggesting that PA represents an initial Aβ prodromal stage of AD. They further suggest that these individuals would develop clinical symptoms, if they live long enough, or have an inherent individual resistence to the toxic effect of β-amyloid [245]. Larger brain and hippocampal values were associated with preserved cognitive function during life despite a high burden of AD pathology [246-248], but the mechanisms that protect from AD are unknown [249-251].

A default hypothesis for AD is that it is part of a "normal aging

process", such that plaques and tangles are secondary to aging or that the primary effect is on synapses and neurons independent of these morphological AD markers. AD is indeed a disease that accompanies human aging, but it is not an inevitable consequence of it [252,253]. However, the suggestion that plaques and NFTs, the morphologic markers of AD, may "cause" this disorder is oversimplified or even wrong, since accumulating evidence indicates that AD pathology represents effect rather than cause or at least a host response to injury, equaling adaptative or neuroprotective reaction [254-256]. A growing body of evidence supports the idea that plaques and NFTs actually define (but not fully represent) the disease process, which involves oxidative stress, neuroinflammation, and many other molecular processes, leading to progressive synaptic, neuronal, and axonal dysfunction and loss [257]. This cascade of pathogenic events is suggested to begin 10 to 20 years before the onset of cognitive decline and other clinical symptoms, but their sequence is still not fully understood [126,258,259].

The AD resiliant group (pathological AD without cognitive impairment) showed preserved densities of synaptophysin-positive presynaptic terminals and dendritic spines compared with the AD-dementia group and increased densities of GFAP-positive astrocytes compared with the AD-dementia group and normal controls [246]. Hence, greater amounts of presynaptic proteins and distinct protein-protein interactions may be components of cognitive reserve reducing the risk of dementia with aging [260]. A recent targeted proteomics study identified a number of factors related to resilience against AD pathology [246]. In conclusion, the aging process that results in loss of synapses and neurons may be far more detrimental for those with little cognitive/brain reserve as compared to those with a high one [261].

Dementia in the Oldest-Old

Neuropathology of AD in the very old demented subjects differs considerably in both intensity and distribution from that in younger age groups [262]. Increased densities of neuritic plaques and NFTs are absent in non-demented patients over age 85-90 [229,263-267], and there is considerable overlap in the pathologies found in demented and non-demented patients [268]. On the other hand, by age 80-85 years, many cognitively unimpaired subjects may have substantial cortical AD pathology [215], 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 ($p=0.076$) [269]. Recent studies suggest that dementia in the oldest-old group (90+ years) is only modestly related to AD, while both cardiovascular and cerebrovascular pathology may cause cognitive impairment in those with low AD pathology scores [175,270,271], and CVLs may contribute to the clinical expression of dementia [272]. However, several clinico-pathologic studies clearly showed that Braak NFT staging remains a significant predictor of cognitive status even in oldest-olds [273,274]. There may be no evidence for some elderly subjects having dementia without an apparent causative morphologic background [270,273], although dementia lacking a known pathologic substrate is extremely rare [275].

In a retrospective clinicopathologic study of 1,100 demented seniors (66% females, MMSE <20; mean age at death 83.3 ± 5.4 SD years) AD pathology increased with highest incidence in the 8th and 9th decade, and slightly decreased after age 90, while the relative prevalence of both AD + minor CVLs and mixed dementia significantly increased with age (7.8 to 32.9% and 0 to 7.%, respectively, $p<0.001$). 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%). 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%, VaD in 11%, DLB in 9%, and dementia of unknown etiology in 13% [270], confirming the notion that a high percentage of demented persons aged 80+ do not meet the pathological criteria of AD or were classified as "dementia of unknown etiology" [97,276,277]. A 90+ study revealed significantly less severe Aβ, αSyn and TP'D-43 pathologies and hippocampal lesions in non-demented subjects, while Aβ distribution showed no esssential differences; non-demented individuals had limited hippocampal tau and neocortical Aβ pathology [241]. Non-AD pathology significantly improved precise differentiation between oldest-old and younger age groups [263].

The Importance of Multiple Pathologies

A major problem is the frequent presence of multiple pathologies in the aged brain that coexist with AD, as CVD, LB pathology, argyrophilic grain disease, hippocampal sclerosis, and others. About two-thirds of aged human brains show non-AD-type neuropathology [229,278-280], which, however, frequently has been missed clinically and could not be identified without neuropathologic examination [72]. Since 50 to 85% of the brains of persons who die aged 80-90+ show appreciable CVLs [281], a specific problem is the impact of CVLs in relation to AD pathology [175,185,237,282-284]. In several autopsy series of very old people, 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 [270] (Table 4).

The burden of vascular and AD type pathologies are considered to be independent of each other, and are consistent with an additive

		Pathologies [%]				
Author	**n**	**AD lesions**	**AD alone**	**AD+ CVL**	**AD+ LBD**	**VaD**
Nolan et al. '98 [285]	87	87	50	34	–	–
Lim et al. '99 [286]	?	AD cases	36	45	22	–
NUN study - Riley et al. '02 [287]		AD cases	57	73/93	–	–
HAAS study - Petrovitch '05 [281]	333	< 60	36	24	–	24
MRC-CFAS (UK) (Fernando-Ince '04) [268]	209 (48% dem.)	70	21	–	–	78
Andin et al. '05 [288]	175 (clin. VaD)	–	72	–	28	
Schneider et al. '07 [237]	141	82.7	30	38	12	12
Jellinger '08 (retrospective) [172]	1700 (dem.)	82.9	48.0	19.0	9.1	10.7
Jellinger (prospective, unpubl.)	180	82.7	48.8	23.9	10.0	7.8
Kovacs et al. '13 [289] (other pathologies 23.2%)	233	100	12	48.9	24	?

Table 4. Mixed pathologies frequent in demented elderly.

or synergistic effect of both types of lesions on cognitive impairment [147,175,185,272,286-291]. The thresholds for vascular and degenerative lesions in distinguishing "pure" VaD or AD from mixed cases have been discussed [274,292,293]. AD pathology alone more frequently accounts for dementia than both microscopic and macroscopic infarcts [294], and in 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 CVD [175,185,295,296]. In a recent autopsy study, global AD pathology significantly correlated to global cognition, whereas infarcts and Lewy bodies did not [234].

The contribution of CVD in neurodegenerative diseased was recently studied in 5715 autopsy cases of the NACC database. For comparison, 210 "unremarkable" cases without cognitive impairment and 280 cases with pure CVD were included. Cases with CVC were older than those without in all groups except for those with hippocampal sclerosis. α-Synucleinopathies, FTLD and prion diseases showed a lower prevalence of coincident CVD than AD patients and those with AD and synucleinopathies revealed a relatively lower burden of their relative lesions then those without CVD in the context of comparable severity of dementia. In conclusion, CVD as a common finding in aged subjects with dementia, is more common in AD than in other neurodegenerative disorders and lowers the threshold for dementia due to AD or synuclein pathologies [282], confirming previous findings [172,175,272,291,293]. Another recent study of 2083 autopsy cases from the NACC database correlating the clinical dementia rate within 2 years before death in 835 subjects showed that the cause of mild to moderate dementia remained uncertain in 14% of the patients. Plaques and tangles independently correlated with cognitive dysfunction and severe small vessel disease, CAA and hippocampal sclerosis were also independently associated with the degree of cognitive impairment, while concomitent CVD strongly correlated with cognitive impairment in the sample selected to represent the AD pathologic continuum, confirming the uncertainty of AD clinicopathologic correlations based only on tangles and plaques [88].

Many studies emphasize multiple confounding pathologies in non-demented elders, in particular CVLs, e.g., small or large cerebral infarctions, lacunes, and white matter lesions in up to almost 10% [230,236,297,298]. Evaluation of 336 cognitively normal (CN) seniors from four studies revealed moderately to frequent neuritic plaque density in 47%, of these 6% also had Braak stages I to VI, medullary, nigral, and cortical Lewy bodies in 15, 8 and 4%, respectively, cerebral microinfarcts in 33%, and high-level microinfarcts in 10%. The burden of brain lesions and comorbidities varied widely within each study but was similar across studies [299].

Among 418 non-demented partizipants of the Religious Order study (mean age 88.5 ± 5.3 years), 35% showed macroscopic infarcts, 8% microinfarcts, 14.8% arteriosclerosis, 5.7% both, only 37.5% being free of CVLs [300]. Up to 75% of CN seniors had various degrees of CAA [298], argyrophilic grains in up to 23% [298], Lewy pathologies in up to 18% [229,230,236,280,301], occasional hippocampal sclerosis [298,301], and mixed pathologies in 7 to 15% [230,280]. Among 100 non-demented elderly, mild, moderate and severe intracranial atherosclerosis was present in 31,17 and 6%, respectively, lacunar state in basal ganglia and/or white matter in 73%, hippocampal sclerosis in 3%, LBs in 5%, tau pathology in brainstem in 60%, and mixed cerebral pathologies in 6%, whereas only 9% were free of CVLs [229]. A recent British non-demented sample (n=53; mean age 81.5 ± 7.4 years) showed maximum score neuritic plaques in 32-49%, NFTs in hippocampus and neocortex in 81 and 30.8%, respectively, white matter lesions in 55-83%, small vessel disease in 45%, infarcts in 13.7%, lacunes in 6%, and cerebral hemorrhages in 10% [302]. A community-based autopsy series from the Viennese VITA study [303] of 233 individuals over 75 years of age (age at death 77-87), in addition to some degree of NFT in 100%. showed Aβ deposits (68.7%), CVLs (48.9%), non-Alzheimer tauopathies (23.2%), TDP proteinopathy (13.3%), and others (inflammation, tumors, etc, 15.1%). Most of these lesions did not increase the probability of the co-occurrence of others, while the number of observed pathologies correlated significantly with AD-neuropathologic changes [289]. A recent cross-sectional study in a community-based sample of 72 cognitively normal older individuals (mean age 74.9 ± 5.7 years) confirmed that a substantial number harbor neurodegeneration without Aβ burden, but association of neurodegenerative lesions with CVD can emerge through non-Aβ pathways within regions most affected by AD [222].

The synergistic interaction between Aβ, tau, and αSyn, accelerating neuropathology and cognitive decline, has been summarized recently [76,304].

Conclusions and Outlook

Increases of biochemical, genetic, and experimental approaches are used for refinement of diagnosis and analysis of the relevant contribution of different disease processes to neurodegeneration in AD and other dementias [305]. Since the majority of degenerative dementing disorders are associated with intracellular and/or extracellular deposition of misfolded proteins, most of them can be diagnosed by morphologic and/or molecular identification of these deposits representing characteristic markers or signposts of particular disorders. Algorithms for the molecular-pathologic classification of sporadic (nongenetic/nonhereditary) forms of neurodegenerative dementias have been proposed [77,78,306]. However, due to variable overlap, these changes may fail to distinguish between cognitively intact aged subjects from those with MCI or preclinical or mild AD [4,8,92,307,308]. These latter groups show a wide variety in intensity and pattern of AD-related lesions and other (vascular) pathologies [230,302]. Although they often differ from "normal" aging, only a small proportion of cognitively intact aged subjects are free of AD pathology, while up to 50% may show AD-related changes or even definite AD pathology [215,232,236,297,309]. Additional challenges arise from frequent coexistence with other pathologies that may have an additive or synergistic effects (Figure 5), although their mutual impact often

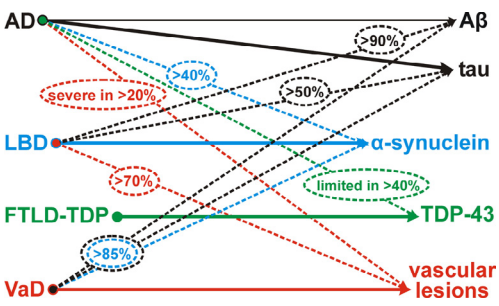

Figure 5. Multiple pathologies in brains of demented seniors. Full arrows point towards the characteristic neuropathology of the respective disease, while dotted arrows point towards neuropathological lesions that are frequently seen in addition to the main pathological hallmark lesions. Approximate percentages are encircled. AD, Alzheimer's disease; LBD, Lewy body diseases; FTLD-TDP, frontotemporal lobar degeneration with TDP-43 pathology; VaD, vascular dementia. Reproduced with permission from [233].

remains unclear. Cohorts with comprehensive neuropathological assessment and multimodal biomarkers are needed to characterize independent predictors for the different neuropathological substrates of cognitive impairment [310].

Neuropathology using immunohistochemistry, molecular biological and genetic methods can achieve a diagnosis or classification in up to 95%, using homogenous and harmonized definitions and standardized inter-laboratory methods, standards for the assessment of nervous system lesions, and considering exact clinical data. Interdisciplinary projects/ initiatives for the standardized assessment of clinical, neuroimaging, biomarker, and neuropathological data are currently under way [39,42,47,311-316]. In the majority of cases except those with known genetic or metabolic backgrounds, however, pathologic examination may not be able to clarify the causes or etiology of most dementing disorders [74], while some conservative authors emphasized that autopsy examination of well-studied cases of AD and other dementias still has a critical role to play [317]. Therefore, the reliabilty and clinical relevance of the current criteria for the neuropathologic diagnosis of neurodegenerative disorders need better qualification and validation in order to find a way out of the "chaos" regarding histological diagnosis of dementia and their clinical implications [1,87]. Molecular genetics, biochemistry and animal models, at least in part reproducing the morphology of human AD and related disorders, have produced a large body of data on the pathogenesis and pathophysiology of these diseases, showing a complex cascade of events leading from preclinical to fully developed neurodegeneration [318-323]. However, both their molecular backgrounds, basic etiologic factors, pathogenic interrelations of various concomitant pathologies, and their impact on the manifestation of AD need further validation. Harmonized techniques are required to increase the accuracy and reproducibility of neuropathological diagnosis as a basis for further personalized treatment and neuroprotection; an enormous challenge for modern neurosciences.

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