Pathobiological Subtypes of Alzheimer Disease

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Keywords

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Abstract

Alzheimer disease (AD), the most common form of dementia, is a heterogeneous disorder with various pathobiological subtypes. In addition to the 4 major subtypes based on the distribution of tau pathology and brain atrophy (typical, limbic predominant, hippocampal sparing, and minimal atrophy [MA]), several other clinical variants showing distinct regional patterns of tau burden have been identified: nonamnestic, corticobasal syndromal, primary progressive aphasia, posterior cortical atrophy, behavioral/dysexecutive, and mild dementia variants. Among the subtypes, differences were found in age at onset, sex distribution, cognitive status, disease duration, APOE genotype, and biomarker levels. The patterns of key network destructions parallel the tau and atrophy patterns of the AD subgroups essentially. Interruption of key networks, in particular the default-mode network that is responsible for cognitive decline, is consistent in heterogeneous AD groups. AD pathology is often associated with

co-pathologies: cerebrovascular lesions, Lewy pathology, and TDP-43 proteinopathies. These mixed pathologies essentially influence the clinical picture of AD and may accelerate disease progression. Unraveling the heterogeneity among the AD spectrum entities is important for opening a window to pathogenic mechanisms affecting the brain and enabling precision medicine approaches as a basis for developing preventive and ultimately successful disease-modifying therapies for AD.

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Introduction

Alzheimer disease (AD), the most common form of dementia in adults that currently affects around 50 million people worldwide, was initially defined as a clinicopathological entity. In terms of neuropathology, AD is defined as a brain disease with deposition of β -amyloid ($A\beta$) in extracellular $A\beta$ plaques and in the vasculature (cerebral amyloid angiopathy/CAA), neuritic plaques (a subset of senile plaques defined by the presence of hyperphosphorylated tau-protein/p-tau), and intraneuronal aggregation of p-tau protein forming neurofibrillary tan-

gles (NFTs). These changes are accompanied by early synaptic loss [1], immune-responsive microglia [2], reactive astroglia [3], neurovascular dysfunction [4], disruption of the blood-brain barrier [5], neuronal loss, and brain atrophy [6]. A neuropathological diagnosis of AD is made according to the updated National Institute of Aging/Alzheimer's Association (NIA-AA) "ABC" criteria [7]. This ABC score for AD neuropathological changes (ADNC) combines "A" for the phase of amyloid plaques [8]; "B" for the NFT stages [9], and "C" for the CERAD neuritic plaque score [10]. These pathological changes, which involve brain regions and neuronal cell types following a characteristic pattern [9] as a result of selective cellular and regional vulnerability to pathological proteins and their spread through the brain [11], present clinically as progressive decline in cognition and other functions.

Classically, AD manifests as a progressive, multidomain amnesic syndrome, but individual patients show variant syndromes, which present major challenges for both diagnosis and monitoring of disease progression [12]. AD is a heterogeneous, multifactorial continuum with several clinically and pathobiologically defined subtypes, currently referred to as Alzheimer clinical syndrome [13]. Its variability in age and clinical presentation is very well known, such as the clinical and morphological differences between early-onset AD (EOAD) that may occur on a monogenic basis [14] and the much more common and apparently sporadic late-onset AD (LOAD) [15, 16]. EOAD is associated with a higher burden of ADNC and a higher rate of neocortical atrophy [17], but shows significant heterogeneity in cognitive presentation and patterns of atrophy/hypometabolism [18].

Regarding variation in the clinical presentation, different phenotypes based on consensus and accepted guidelines have been determined, which show that the amnesic syndrome [19] is more common than nonamnesic presentations [20], such as posterior cortical atrophy [21], logopenic primary progressive aphasia (LPPA) [22, 23], and the behavioral variant of AD [24, 25], while the corticobasal syndrome (CBS) subtype of AD shows an atypical distribution of ADNC [26].

Clinicopathological Diversity of AD Variants

Recent progress in biomarker research and wider availability of postmortem data has enabled the identification of pathophysiologically defined subtypes of AD, based on neuropathological, neuroimaging, and in vivo

biomarker data. With the new definition of AD as a biologically defined spectrum, using the NIA-AA research framework [13], it is now possible to review the pathobiologically defined subtypes of AD [27]. Research consensus guidelines have been proposed for the intravital biologically based categorization termed "ATN," which uses flexible combinations of in vivo biomarkers for A β deposition (A), tau pathology (T), and neurodegeneration (N); they include cerebrospinal fluid (CSF) or plasma biomarkers, PET, and functional and structural MRI. The biomarker profiles and categories of the Alzheimer continuum referring to ADNC have been summarized recently [28]. The risk of progressive cognitive deterioration differs considerably between the various subtypes: A-N- < A+N- < A+T-N+ < A+T+N+, the A+T-N+ cases with the worst prognosis versus negative (A-T-N-) ones [29].

Several subtypes of AD have been proposed based on clinical, biological, and neuropathological features that have been evaluated in a systematic review and meta-analysis [27]. A seminal study of 889 brain autopsies classified 3 AD subtypes based on postmortem NFT density: typical AD with balanced NFT counts in neocortex and hippocampus (75% of cases), hippocampal-sparing (HcSp) AD, with NFT counts predominantly in association cortices (11%), and limbic-predominant (LP) AD, with NFT mainly involving the hippocampus (14%) [30]. These neuropathological subtypes had also different clinical phenotypes, with different ages at onset and rates of progression. Patients with HcSp-AD had earliest age at onset, a higher proportion of men, and progressed more quickly than typical AD, while LP-AD patients were older, had a higher proportion of women, and progressed more slowly. Disease duration of LP-AD and typical AD cases was similar, while the Mini-Mental State Examination (MMSE) was lowest in the HcSp form but did not differ from typical AD. The age at death for the LP form was highest, while patients with HcSp-AD were youngest, reflecting that the latter is the most aggressive. NFT accumulation in the nucleus basalis of Meynert may underlie more widespread and severe cholinergic deficits in young-onset AD, in particular with HcSp ($p=0.3$) and typical AD ($p<0.001$) and APOE ϵ 4 allele ($p=0.3$) [31]. This is coherent with the possible contribution of TDP-43 pathology, hippocampal sclerosis, and the microtubule-associated protein tau (MAPT) H1H1 genotype to LP-AD, factors related to atrophy restricted to the temporal lobes, older age, and slower disease progression. APOE ϵ 4 carriers more frequently had LP and typical AD, whereas noncarriers more frequently had HcSp-AD. APOE ϵ 4 has

Table 1. Major characteristics of Alzheimer disease (AD) subtypes [34]

Characteristics	HcSp-AD	LP-AD	Typical AD
Total, <i>n</i>	79 (8.2%)	85 (8.9%)	769 (82.5%)
Females, <i>n</i>	47 (59.5%)	55 (64.7%)*	520 (67.5%)*
Age			
At death	76.3±8.6	84.9±3.8*	81.3±9.2*
At onset	68.0±10.0*	73.8±6.4*	79.7±3.8***
Disease duration	7.4±3.6**	4.8±2.6***	9.1±4.3*
Mean final MMSE	10 (<i>n</i> = 20)	11.5 (<i>n</i> = 16)	4.6 (<i>n</i> = 78) ^a
Median Braak NFT stage (range)	4.5 (2–5)	4.5 (3–5)	5.6 (5–6)
Cerebrovascular pathology, <i>n</i>	27 (34.2%) ^b	35 (41.1%)	286 (36.4%) ^b
Lewy body pathology, <i>n</i>	19 (24.9%) ^a	3 (3.5%)	63 (8.2%)

Means ± SD, *n* (%), or medians (ranges). MMSE, Mini-Mental State Examination; NFT, neurofibrillary tangles; HcSp-AD, hippocampal-sparing AD; LP-AD, limbic-predominant AD. * *p* < 0.01, ** *p* < 0.001, *** *p* < 0.001, vs. HcSp-AD, ^a *p* < 0.01 vs. other forms, ^b *p* < 0.01 vs. LP-AD.

been associated with a lower volume in the hippocampus and adjacent regions [32, 33]. Therefore, APOEε4 negativity may increase resistance of the hippocampus against tau pathology. Vascular co-pathology (ranging from 16 to 36%) was highest in the LP and lowest in the HcSp cases, while Lewy co-pathology was lowest in the latter type. These data were largely confirmed by another study in 933 autopsy cases of AD, all with neuritic Braak stage >4 (Table 1 [34]). Typical AD in our cohort was more frequent than in the Mayo series (82.5 vs. 75%), while the other 2 subtypes were slightly less frequent. MA-AD was not considered in this study. The LP-AD cases shared some morphological characteristics with primary age-related tauopathy (PART) [35], although this was not confirmed later, which emphasizes significant pathological differences versus LP-AD and suggests that it may not merely be a variant of AD [36]. PART, predominantly involving people aged >85 years and associated with mild-to-moderate cognitive impairment [37, 38], is morphologically characterized by tau pathology restricted to the medial temporal lobe (Braak stages 0–IV), relative absence of amyloid (Thal Aβ phases 0–2), total absence of neuritic plaques, and rare CAA [39]. neurofibrillary changes in PART are identical to those in classical AD, with both 3 and 4 repeat (3R and 4R) tau isoforms [40]. PART is considered either a prodromal form or a subtype of AD [41]. MAPT H1H1 genotype frequency is high in both PART and LP-AD, and similar to typical AD, while the APOEε4 carrier state is low in PART [42]. In PART, the lack of Aβ oligomers is responsible for less severe tau aggregation and, thus, for lower Braak stages and less cognitive impairment since Aβ oligomers have been shown

to potentiate tau aggregation by promoting tau seed uptake [43]. While the incidence of classical AD increases from the 7th to the 9th decade and shows a mild decrease later, the frequency of PART increases after 85 years of age [44].

In the Vienna series, the proportion of females was highest in typical AD (67.5%) and lowest in HcSp-AD (59.5%). Similar to the Mayo series, age at disease onset and death was significantly higher in LP than in typical AD (*p* < 0.01), and significantly lower in HcSp-AD. Final MMSE scores were lowest in typical AD, and they did not essentially differ between the 2 other types, whereas in the Mayo series, the final MMSE scores were lowest in the HcSp form and slightly higher in typical AD cases. Among co-pathologies, cerebrovascular lesions were more frequent in our cohort (34.2–41.1%) and most frequent in LP-AD cases. Lewy body (LB) pathology was highest in HcSp forms (24%, due to the frequent association of dementia with LB), and much lower in the 2 other subtypes (3.5 and 8.2%, respectively), thus less frequent than in the Mayo series.

Neuroimaging Findings in AD Subtypes

The 3 AD subtypes, based on the distribution of NFTs and corresponding brain atrophy, have also been identified by neuroimaging studies using structural MRI [45–48]. Brain atrophy corresponds well with NFT topography, and amnesic and nonamnesic symptoms correspond to regions of neuronal injury and correlate to neuronal hypometabolism [30, 45, 49].

Fig. 1. Main factors and characteristics of the 4 main subtypes of AD. AD, Alzheimer's disease; NFT, neurofibrillary tangle; WMH, white matter hyperintensity; CAA, cerebral amyloid angiopathy.

Recent MRI studies have consistently identified 4 categories of brain atrophy: both hippocampal and cortical atrophy, hippocampal only, cortical only, and no or minimal gray matter atrophy, which, however, shows comparable clinical severity [50–55]. Compared with the other 3 subtypes, MA-AD showed an intermediate age at onset. Despite not presenting with significant atrophy but having AD CSF biomarker levels (CSF p-tau increased and A β decreased), this group fulfilled the diagnostic criteria

for AD but had a slow rate of disease progression. This was concordant with other studies [49, 56, 57].

Because the 4 subtypes did not differ substantially in disease duration, the age at the time of MRI was the lowest in HcSp-AD and the highest in typical and LP-AD, with MA-AD in between, although timing of MRI studies differed considerably in postmortem studies [27, 48]. Among 175 AD patients and 81 healthy controls from the ADNI-1 study, 50.9% were typical AD, 17.1% LP-AD,

16.1% HcSp-AD, and 15.4% MA-AD [52]. Another MRI study of brain atrophy subtypes that may predict long-term cognitive decline in AD distinguished HcSp, cortical, homogenous atrophy, and “no evidence of brain atrophy” subtypes. The MA-AD subtype was associated with an increased risk of developing the clinical AD over time [58]. A recent study using MRI, tau, and A β PET based on cortical atrophy revealed 3 subtypes of AD: medial temporal (53%), parietal dominant (22%), and diffuse atrophy (23%), while A β deposition did not differ across the subtypes [59], suggesting a typical pattern of tau spread, with NFTs developing in the entorhinal cortex and then processing to the association cortices; the MA form would be the earliest presentation, which progresses via the LP-AD finally to typical AD (Fig. 1). However, there is growing evidence supporting the alternative “distinct subtype hypothesis,” which suggests actual heterogeneity of disease progression [30, 60–62].

Studies of the tau PET patterns in 260 A β -positive patients with mild cognitive impairment (MCI) or dementia revealed the greatest tau load in HcSp-AD (frontoparietal predominant) and typical AD (temporal predominant), while LP patients showed excessively higher entorhinal tau load. These data suggest that structural MRI can be used to identify biologically and clinically meaningful subtypes of AD [63]. Tau pathology is closely associated with sites of neurodegeneration [24, 64, 65]. Typical AD had the most prominent and greater white matter hyperintensity burden, which may be due to wallerian degeneration induced by cortical tau pathology [66], small vessel disease, or both [67, 68]. The HcSp patients had often nonamnestic disease presentation and most rapid cognitive decline. Recent studies showed that flortaucipir PET reflects neuritic Braak stages IV or greater neuropathology, thus being a reliable biomarker of underlying NFT pathology [69].

Tau pathology and neurodegeneration at the molecular level can be sufficient to disrupt key brain networks, which could induce symptoms in the absence of overt brain atrophy of the medial temporal lobe in MA-AD that shows memory impairment comparable to LP and typical AD [48, 52, 61]. This is supported by the finding of reduced metabolism in the parietal cortex in these patients [70]. The devastation of the medial temporal lobe may explain memory impairment [45, 47, 49, 56, 57, 61]. Distinct signature patterns of network destruction, which parallel the NFT and atrophy pattern of the 4 subtypes, have been demonstrated, and are consistent with isocortical Braak stage V [52]. The cortical areas of the default-mode network are involved in typical, LP-, and MA-AD,

while 3 major networks in posterior brain regions (frontoparietal, visual, and default-mode networks) are affected in MA-AD [52]. Hence, disruption of the default-mode network is a consistent damage in heterogeneous AD groups [47, 71]. These findings support the *distinct subtype hypothesis*, with pathology spreading through the brain in a different manner in these subtypes, as opposed to the *staging hypothesis* [30, 52, 60].

Typical AD had higher A β plaque counts in occipital regions than LP-AD [30], which showed greater A β PET binding in frontal and parietal cortices than typical AD [46]. However, in contrast to specific tau accumulation and brain atrophy patterns among AD variants, A β accumulation appears rather diffuse and is similar across groups, with the exception of the MA group [72, 73]. Since A β deposition develops decades prior to the first signs of cognitive impairment [74], it might be possible that it initially develops differentially in AD variants before reaching a plateau at a relatively early stage [11]. Autopsy studies have found that tau pathology is more closely related to atrophy and clinical symptoms than A β pathology [75]. However, the synergism between A β deposition and NFT neurodegeneration may be a better predictor of cognitive decline or disease progression than either pathology alone [76]. The revised NIA-AA guidelines for the pathological diagnosis of AD, which take A β Thal phase, neuritic Braak stage, and co-occurrence of pathological tau within A β -containing neuritic plaques into account, are now a widely accepted guide for assessing ADNC severity [7]. CAA seemed to make a stronger contribution to HcSp- and MA-AD, whereas hypertensive arteriopathy had a stronger influence on typical AD and LP-AD.

HcSp-AD cases have been found to have the highest level of education, while MA-AD patients had the lowest, suggesting that high education may be one of the factors protecting the hippocampus and thus contributing to the fact that LP-AD may be unmasked and may contribute more to the clinical manifestation of the disease. The theory of cognitive reserve suggests that education is beneficial for the brain by forming more efficient and pathology-resistant networks; it may act as surrogate for or act in synergy with cognitive or social engagement [77, 78]. This suggests that people with higher reserve can cope with brain pathology better [79]. More severe neurodegeneration and more aggressive disease progression in HcSp-AD [30, 36, 47, 51, 80], and the absence of hippocampal brain atrophy in the MA form, which has a lower level of reserve, support this hypothesis [27]. A higher cognitive reserve has been associated with lower cortical

Table 2. Atypical variants of late- and early-onset Alzheimer disease (modified from [11])

AD subtype	Clinical presentation	Pathology	Progression	CSF A β and tau levels
Typical LOAD (50–75%)	Amnesic/ nonamnesic	Both hippocampal and cortical (“both impaired”)	Typical AD	Typical AD
Limbic-predominant LOAD (15–35%)	Amnesic	Medial-temporal lobe (“hippocampal”)	Slower	Similar
Hippocampal-sparing LOAD (10–25%)	Nonamnesic	“Cortical,” medial temporal lobe sparing	Faster	Similar
Minimal-atrophy LOAD (10–17%)	Unclear	Minimal	Slowest	A β $\uparrow$, tau $\downarrow$
Typical EOAD (75%)	Amnesic/ nonamnesic	Hippocampal and cortical	Typical AD	Similar to typical AD
Atypical EOAD (25%)	Nonamnesic	Posterior cortical	Faster	Similar to typical AD

AD, Alzheimer disease; LOAD, late-onset AD; EOAD, early-onset AD.

tau-PET binding, which has been interpreted as brain reserve/higher cognitive reserve possibly contributing to avoid tau aggregation [81].

A recent study using diffusion tensor imaging and latent Dirichlet allocation for the white matter found a different composition profile of latent impairment factors, which indicated heterogeneity and subtypes of AD through white matter impairment factors. The latent factors have distinct impact on cognitive decline: for executive function, the temporofrontal compared with the parietal factor, while the long-fiber factor was most associated with executive function decline. Three factors (temporofrontal, parietal, and long-fiber factor) showed almost equal effect on the memory decline rate. Thus, white matter impairment factors contribute to investigating heterogeneity and subtypes of AD [82]. Another recent study of 1,677 dementia cases from the National Alzheimer’s Coordinating Center Registry separated “tangle-intensive” and “plaque-intensive” cases from “classic AD,” which indicates that neuropathology does not directly reflect current consensus recommendations [83].

The APOE genotype was found to affect the AD subtype. Specifically, APOE ϵ 4 was more associated with the long-fiber bundle factor and APOE ϵ 2 with temporofrontal factor, confirming the heterogeneity of AD. Genetic research in AD subtypes also focuses on the MAPT H1H1 genotype, which is increased in LP-AD compared to the others [30, 36]. However, another study reported its highest frequency in typical AD, followed by the 2 others [48]. These findings suggest that the MAPT H1H1 genotype may be important for the medial temporal predilection of tau pathology. The proportion of APOE ϵ 4 is elevated in amnesic but not in aphasic manifestations of AD. It is an

anatomically selective risk factor that increases the vulnerability in memory-related medial-temporal areas rather than language-related areas [84].

A recent meta-analysis of 24 studies calculated the pooled frequency of the 4 AD subtypes. Typical AD, characterized by tau pathology and atrophy in both hippocampus and association cortex, is the most frequent subtype, with a pooled frequency of 55%. LP-, HcSp- and MA-AD had a pooled frequency of 21, 17, and 15%, respectively [27]. These data depended on the algorithm used for biological and nonbiological subtyping, such as age at onset and death, disease duration, education years, MMSE, clinical dementia rating, APO status, and CSF biomarkers (see Table 2 [11]).

Neuropathology of Other Clinical AD Variants

Pathologically proven AD shows a broad spectrum of clinical manifestations beyond the classical progressive amnesic-predominant syndrome. Clinicopathological studies have identified a number of atypical nonamnesic syndromes generally referred to as atypical or focal AD [12, 85, 86]. The major atypical variants of EOAD and LOAD are presented in Table 2. More recent studies have defined a larger variety of atypical clinical syndromes, including LPPA [22, 23, 87], posterior cortical atrophy [21], CBS [26, 88–90], and behavioral/dysexecutive syndrome resembling the behavioral variant of frontotemporal dementia (bvFTD) [24, 25], and a nonamnesic AD with TDP-43 pathology [20]. Atypical clinical variants of AD often show a younger age at onset and fewer associations with the APOE ϵ 4 genotype compared to typical amnesic

forms [30, 91]. Recent studies in a large postmortem series investigated the clinical relevance of regional NFT pathology with regard to various clinical variants of AD and domain-specific clinical representations [92]. Individuals with LPPA showed significantly higher NFT density in the superior temporal gyrus relative to those with an amnesic syndrome and to other atypical variants, while those with CBS revealed higher NFT density in the perirolandic cortices, namely the primary motor and somatosensory cortex, but less in the superior temporal cortex. However, the neuritic Braak stage and the Thal amyloid phase were similar to amnesic AD. ADNC had a predilection for left language regions that showed the most severe atrophy in primary progressive aphasia [93]. The CBS subtype of AD had greater neuronal loss in the substantia nigra, which may contribute to parkinsonism that is not a typical feature of classic AD [26]. In a series of pathologically confirmed nonamnesic cases, 44% had typical AD pathology and were TDP-43 positive, which, however, did not essentially influence the clinical and anatomical features of AD [20]. Both behavioral and dysexecutive AD are distinguished by temporoparietal-predominant atrophy, but frontotemporal lobar degeneration-tau and -TDP-43 pathology occur in various degrees and several co-pathologies, such as CAA, dementia with LB, and argyrophilic grain disease [24], whereas others found a higher NFT burden in the subiculum [92]. In the Mayo series, posterior cortical atrophy, LPPA, and bvFTD variant were more common in HcSp-AD than in LP-AD and typical AD [30, 46, 94], specific functional consequences of regional tau/NFT accumulation, the mapping of which may increase the understanding of functional-clinical manifestations of AD.

The neurobiological features underlying AD subtypes are largely unknown and cannot be explained by A β pathology, because the distribution of A β PET retention is virtually the same in all subtypes [72]. MA-AD is less affected by tau pathology but also A β positive. This suggests that multiple subtypes are in reality one of the same AD continuum of a single disease type [24].

More Indicators of AD Heterogeneity

The original ADNI (Alzheimer's Disease Neuroimaging Initiative) data considered 5 diagnostic groups in a total 658 patients (AD: $n = 110$, late MCI: $n = 133$, early MCI: $n = 148$, significant memory concern: $n = 94$, and cognitive normal: $n = 173$). Clustering the cohort by applying a novel big data analysis strategy [95], a recent

study suggested a different set of 6 subtypes which present different clinical patterns and potential biomarkers: "healthy" ($n = 121$), "affective MCI" ($n = 101$), "anosognosia dementia" ($n = 54$), "worried well" ($n = 148$), "uncompensated MCI" ($n = 136$), and "insightful dementia" ($n = 98$) [96].

A study comparing cognitive disorders with MRI and PET findings in 146 EOAD subjects and 395 age-matched controls differentiated 4 clusters: cluster 1 (memory-predominant impairment) presented atrophy/hypometabolism in medial/lateral temporal, lateral parietal, and posterior cingulate, and cluster 2 (memory/visuospatial predominant) involved medial temporal, temporoparietal, and frontal cortices; cluster 3 (memory, language, and executive function) and cluster 4 (globally impaired) both showed atrophy and hypometabolism throughout the brain. Cluster differences between visuospatial/executive domains were significant, indicating heterogeneity in cognitive presentation among amnesic EOAD subjects and patterns of atrophy/hypometabolism in each cluster in agreement with the observed cognitive phenotypes, suggesting phenotypic variation [18].

Another study classified 4,050 people with LOAD into 6 groups based on their cognitive functioning in 4 domains: memory, executive and visuospatial functioning, and language, and then genetic data were used to find biological differences among cognitively defined subgroups [97]. The largest group (39%) had fairly similar scores in all 4 domains, followed by those (27%) who had significantly lower memory scores; smaller groups had substantially lower language scores (13%), others lower visuospatial functioning scores (12%) and lower executive functioning scores (3%), while another 6% had 2 domains that were substantially lower than the other scores. Single nucleotide polymorphisms (SNPs; $n = 33$) were found throughout the genome, where the genetic association was very strong for 1 of the 6 subgroups, indicating that AD is not a single homogenous condition.

The Challenges of Co-Pathologies

AD pathology rarely occurs in isolation, and community-based neuropathological studies have shown that complex constellations of underlying pathologies may lead to cognitive decline. The number of possible combinations or comorbidities increases in the aging brain, and frequently mixed pathologies ensue [38, 44, 67, 98–100]. Patients with ADNC often have concomitant pathologies, such as cerebrovascular disease (CVD), LB pa-

thologies, and/or TDP-43 proteinopathy [101, 102]. In a consecutive series of 1,700 elderly demented patients and those with the clinical diagnosis of AD, ADNC were present in 82.9% of all demented and in 92.8% of those with the clinical diagnosis of AD, but only half of them (41.1 and 47.6%, respectively) showed pure ADNC (ABC 3/3/3), while all the others were either atypical AD forms or subtypes (including PART; 7 and 6%, respectively) or showed additional CVD, cerebral hemorrhage, LB, or other mixed pathologies, while vascular dementia in this cohort accounted for only 10.7 and 3.3%, respectively, and other non-AD pathologies were seen in 17 and 7.2%, respectively [103]. An earlier study of AD in clinical trials revealed pure ADNC in only 31% and multiple pathologies in 63%, while no pathological changes were seen in 1% [104]. A review of 12 community-based studies with 3,574 patients, irrespective of the clinical symptoms, reported a frequency of ADNC between 19 and 67%, of LB pathologies between 6 and 39%, of vascular pathologies between 28 and 70%, of TDP-43 proteinopathy between 19 and 75%, of hippocampal sclerosis between 3 and 13%, and, finally, of mixed pathologies between 8 and 70% [99]. Data from the Religious Orders Study and Memory and Aging Project cohort showed that about 50% of persons diagnosed with probable AD had mixed pathologies (AD, dementia with LB/Parkinson disease, and CVD). Among 447 patients with probable AD, only 3.13% showed pure ADNC, 27.3% AD + CVD + other, 3% AD + CVD, 7.6% AD + other degenerative lesions, and 47% AD + CVD + other neurodegenerative changes [100]. Lower cognitive reserve and small-vessel disease in strategic white matter areas [62] could increase network vulnerability to tau pathologies and neurodegeneration in MA-AD [105]. Similar comorbidities in 1,153 patients with the clinical diagnosis of AD were reported recently [106], and among 673 autopsy cases, 301 of which were demented, the majority of the demented cohort showed mixed pathologies [67]. LP age-related TDP-43 encephalopathy neuropathological change (LATE-NC) was present in approximately 57% of AD cases and was associated with accelerated cognitive decline and accelerated disease progression [107]. The strong association between hippocampal sclerosis and TDP-43 has been confirmed by the fact that TDP-43 is increased in typical and LP-AD compared to HcSp-AD [30, 94]. On the other hand, among 172 autopsy-proven AD cases, 19% were classified as nonamnesic, 69% of which had typical ADNC and 44% were TDP-43+; 31% were HcSp-AD, of which 36% were TDP-43+, but no LP-AD were found [20]. However, clinical presentation of

AD seems to be driven by subtype and not by TDP-43 [94]. This is strengthened by a recent study of 46 autopsy-confirmed AD cases, 63% of which exhibited LATE-NC (AD+) and a higher burden of p-tau (AT8). No association between AT8 with LATE-NC score was revealed, but the higher intensity of AT8 pathology indicated possible progression of the disease compared to AD cases, whereas the presence of LATE-NC was not associated with differences in cognitive scores in AD.

A recent clinicopathological study using data from the National Alzheimer's Coordination Center showed that 1,854 participants had a clinical diagnosis of AD and ADNC at autopsy (confirmed AD); 204 with a clinical AD diagnosis had no ADNC (AD mimics), and 253 participants with no clinical AD diagnosis had ADNC (unidentified AD). Compared to confirmed AD cases, AD mimics (e.g., frontotemporal lobar degeneration-tau, hippocampal sclerosis, and cerebrovascular pathology) had less severe cognitive impairment, while unidentified AD participants displayed more parkinsonian signs, depression, and behavioral problems. This study emphasizes the importance of developing a complete panel of biomarkers as a tool to promote clinical diagnosis, as clinical phenotypes that are typically associated with diseases other than AD may result in inaccurate diagnosis [108].

A comparative study of clinical and neuropathological diagnoses of AD in 3 epidemiological samples reported a sensitivity of probable AD of 93% [109]. Meta-analysis of 20 (out of 1,189) studies to distinguish autopsy-verified AD from other dementias or healthy controls showed a sensitivity of 85.4% (95% CI 80.8–90%) and a specificity of 77.7% (95% CI 70.2–85.1%). Values were higher for neuroimaging procedures and slightly lower for CSF biomarkers, while the combination of both resulted in higher values [110]. These data are related to 2 factors: (1) the various subtypes or variants of AD, as described above, and (2) the high frequency of comorbidities in elderly persons that may cause difficulties in the clinical diagnosis of AD. A recent study showed that antemortem ¹⁸F-flortaucipir PET is able to identify the underlying presence of tau (NFT) pathology at the B3 level and a high level of ADNC per the NIA-AA criteria consistent with a neuropathological diagnosis of AD [111].

In summary, recent community-based neuropathological studies have demonstrated that the complex constellations of the underlying pathologies may lead to cognitive decline, and that the number of possible combinations/comorbidities increases in the aging brain [38]. All these concomitant pathologies may be especially harmful to individuals with low cognitive reserve such as patients

with MA-AD. Total burden of comorbid pathological abnormalities, rather than any single lesion, is the most relevant determinant of cognitive impairment, often despite a clinical diagnosis of “only” AD [112].

Conclusions and Perspectives

AD is a multifactorial disorder, the clinical and morphological heterogeneity of which is documented by several subtypes that have a distinct signature of network disruptions associated with their atrophy pattern probably reflecting the differential spread of NFT pathology and different vulnerability pattern of affected brain regions. These facts are substantially related to 3 important factors, that is, risk factors, protective factors, and concomitant pathologies. The balance between risk and protective factors determines brain cellular and regional vulnerability, which contributes to differential spatial manifestation of pathologies and potential disease-relevant lesion patterns, and eventually leads to divergent clinicopathological presentations of AD. The severity dimension corresponds to the “N” category in the new A/T/N classification for biomarkers [113], indicating that the Alzheimer clinical syndrome includes several pathobiologically defined entities or subtypes, which are clinically and morphologically different. This heterogeneity is due to multiple pathogenic factors, for example, “upstream” genotypes causing comorbidities, “downstream” disease-modifying gene variants (MAPT, H2 haplotype, APOE, TREM, and GRN variants) which induce misfolding tau, A β , TDP-43, and others, the synergetic or additive action of which results in various disease phenotypes [114]. It is possible that factors such as brain resilience may help compensating for these pathologies up to a certain level. However, a combination of risk factors may knock out these compensatory effects. In the absence of these risk factors, brain resistance mechanisms may more efficiently preserve vulnerable cell populations and brain regions, and reduce the vulnerability of key brain networks. It has been suggested that individuals should be identified who have connectivity patterns resistant to the initiation or spread of neurodegeneration. This may be an important factor underlying incomplete penetrance of genetic mutations, differential gene expression across brain regions, or other substrates such as association with minimal or no comorbid abnormalities [115]. Furthermore, compensation strategies could be used in HcSp- and MA-AD, because the learning and encoding capacity in these subtypes is partially spared

[61]. The prevalence of biological AD with its various subtypes and variants is greater than clinical probable AD at any age, in particular at 85+ years of age [13]. Therefore, recent studies have shown that different individuals with *typical* AD may have distinct biochemical features of tau that contribute to the clinical heterogeneity of AD [116]. These facts and the increasing incidence of AD illustrate its consequences on public health. In order to increase the sensitivity and specificity of the new ATN biomarker system, more extensive clinicopathological studies in well-defined populations will be necessary, with postmortem studies using the updated NIA-AA criteria. Neuropathological studies should use a wide range of molecular pathological methods and should evaluate multiple CNS regions. An optimal and less cost-effective strategy would be to screen specifically neurodegeneration-related proteins and to examine their cross reactions. Similar proposals have recently been published for validating the criteria for the diagnosis of 4R tauopathies [117]. Therefore, interdisciplinary studies to improve our knowledge about the pathogenesis of the heterogeneous manifestation of AD and to promote methods for its early diagnosis as the basis for further preventive and successful disease-modifying therapeutic measures are urgently needed.

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