Review

Towards a Better Diagnosis and Treatment of Dementia: Identifying Common and Distinct Neuropathological Mechanisms in Alzheimer's Disease and Vascular Dementia

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Towards a Better Diagnosis and Treatment of Dementia: Identifying Common and Distinct Neuropathological Mechanisms in Alzheimer`s and Vascular Dementia

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Abstract: Alzheimer's disease (AD) and vascular dementia (VaD) together contribute to almost 90% of all dementia cases leading to major health challenges of our time with a substantial global socioeconomic burden. While in AD, the improved understanding of Amyloid beta (Aß) mismetabolism and tau hyperphosphorylation as pathophysiological hallmarks has led to significant clinical breakthroughs, similar advances in VaD are lacking. After comparing the clinical presentation, including risk factors, disease patterns, course of diseases and further diagnostic parameters for both forms of dementia, we highlight the importance of shared pathomechanisms found in AD and VaD: Endothelial damage, blood brain barrier (BBB) breakdown and hypoperfusion inducing oxidative stress and inflammation and thus trophic uncoupling in the neurovascular unit. A dysfunctional endothelium and BBB lead to the accumulation of neurotoxic molecules and Aß through impaired clearance, which in turn leads to neurodegeneration. In this context we discuss possible neuropathological parameters, which might serve as biomarkers and thus improve diagnostic accuracy or reveal targets for novel therapeutic strategies for both forms of dementia.

Keywords: Alzheimer`s; vascular dementia; neurovascular unit; neurovascular coupling; impaired blood brain barrier; neurotoxic metabolites; endothelial damage

1. Introduction

Dementia has emerged as one of the top public health challenges of our time. Due to the aging of the world population and the lack of available causative therapies, the number of affected individuals, estimated at 55 million worldwide by the WHO in 2021 [1], is anticipated to reach approximately 78 million by 2030 and 139 million by 2050. The global financial burden has already outpaced cancer and heart disease [2] with costs of US$ 1.3 trillion in 2019 and may rise to US$ 2.8 trillion by 2030. Although the anticipated "dementia epidemic" has forced world leaders to develop national plans dealing with the tremendous socioeconomic impact and to enhance schemes of research funding, the development of novel treatment strategies, which span the translational gap

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from promising preclinical results to sustained improvement or even prevention of cognitive decline in patients, remains challenging.

The reasons for this long-lasting failure to gain significant progress in new treatment options, are complex. The term "dementia" describes a syndrome of decline in several cognitive domains, which always includes memory deficits and which is severe enough to interfere with independent living [3]. Some consensus was found, which neuropsychological test batteries to use in clinical - and experimental research. However, categorization into different dementia sub-types on the basis of the clinical and neuropsychological phenotype alone is demanding and underlies a constant realignment process depending on new evidence. Thus, AD and VaD are not well defined, neither clinically nor neuropathologically [4].

Initially, the discovery of the amyloid precursor protein and its metabolism leading to different variants of Aß peptides as the core features of the amyloid cascade hypothesis [5] and the parallel identification of the microtubules-associated tau protein originating and accumulating in transentorhinal and hippocampal neurons [6] has dominated the pathophysiological research on AD. However, it has recently become accepted that by the time when neurodegeneration in AD has resulted in first clinical symptoms, additional pathologies in the brain, which interact with Aß and tau pathology and can be traced back to distinct molecular and cellular processes, have emerged [7]. Traditionally AD and VaD have been treated as two different disorders. However, there is evidence that the largest proportion of dementia cases have mixed pathology, comprising features of AD (amyloid plaques and neurofibrillary tangles) as well as ischemic lesions [8,9]. This has initiated a debate [10–12], if vascular dysfunction may be causal or an effect of AD, which for many years in a predominant cell-centric view of AD have been purely attributed to the accumulation of the two key molecules tau and Aβ [13]. In addition, it is generally accepted that in particular for AD additional pathologies frequently co-occur including the TAR DNA-binding protein 43 (TDP-43), Lewy body pathology or hippocampal sclerosis [14–16]. Both proteinopathies are well known to aggravate neurodegenerative processes in AD [17] but also play a role in VaD [18].

In fact, AD and VaD depict many similarities on different levels: (1) Epidemiological studies show that almost all risk factors for AD reported so far have a vascular component which reduces cerebral perfusion [10,19,20]. (2) All approved medication to symptomatically treat AD also improve cerebral perfusion [21]. (3) Cerebral capillary degeneration has been shown to be present in practically all brains of AD participants examined postmortem and in cortical biopsy material from pathologically confirmed AD [22–24].

Targeted therapies beginning to enter clinical practice make a deeper understanding of biomarker classification, thorough diagnosis, identification of co-pathologies and biologically based staging of AD and VaD necessary. We thus discuss in this review relevant common and distinct neuropathological mechanisms in both disease entities. We first highlight the clinical presentation, including risk factors, disease patterns, course of diseases and further diagnostic parameters. We then focus on the known pathology of both forms of dementia and review neuropathological parameters, which might serve as (new) biomarkers, helping to improve diagnoses, or which may be even new anchor points for the development of novel therapeutic strategies.

2. Methods

For this narrative review we searched PubMed for studies comparing clinical presentation, diagnosis and treatment as well as pathological features in AD versus VaD. The index date for this review with latest update is November 7, 2024. Numbers, percentages and other numerical data provided here are true regarding this index date. We first generally researched for the research terms "differences and similarities between AD and VaD" (121 studies found) and "pathology comparing Alzheimer` and vascular dementia" (14 studies found). We then prioritized in particular studies comparing AD versus VaD on clinical and pathological features over studies examining only one of the two pathologies. We in particular included results from clinical data prioritizing randomized studies and studies with pathological confirmation of disease entities. We then searched for the descriptive categories of the Common Alzheimer`s Disease Research Ontology (CADRO [25])

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comparing results found in AD and VaD. These categories included vasculature, vascular lesions, amyloid, tau, apolipoprotein E (ApoE), transmitter receptors, inflammation, oxidative stress, neuronal cell death, synaptic plasticity/ neuroprotection, metabolism and genetic regulators. We also focused on (macro-) anatomical differences and specific locations comparing AD and VaD for the different features.

Limitations

Although this review fills the gap and stands alone by reviewing the current literature of preclinical and clinical studies and by comparing pathomechanisms of the two most common forms of dementia, it also shows the lack of methodological uniformity among studies including diagnostic criteria. Performing prospective randomized studies is often limited due to the current situation, that AD can still be only definitely diagnosed post-mortem. Thus, many studies are only executed based on clinical diagnosis and with absence of specificity or without autopsy confirmed diagnosis of the underlying neuropathology. Further biases e.g. of inclusion/exclusion criteria are discussed in the corresponding chapters (e.g. end paragraph of "prevalence and risk factors").

3. Clinical Features

3.1. Prevalence and Risk Factors

Age is the most important risk factor for developing dementia. The risk of developing VaD doubles every 5.3 years, an exponential rise which is slightly less pronounced than in AD, where rates double every 4.5 years [26]. Furthermore, around 15-30% of stroke survivors develop dementia within 3 months after stroke [27]. Having a stroke, also increases the risk of developing dementia in the long-term, with about 20-25% of stroke survivors revealing a delayed form of dementia [27]. Discussions raised if post-stroke dementia is a pathology on its own, as the development of this disorder is very heterogenous in its nature. E.g. for some cases it remains unclear, if the stroke has just unmasked an already present cognitive impairment, whether only the cerebrovascular pathology is responsible for the cognitive decline or whether the cerebrovascular pathology fortified a neurodegenerative picture as seen in AD. A long-term autopsy follow-up study in stroke survivors aged over 75 years [28] claimed that vascular but not degenerative dementia was the cause of the dementia in 75% of the cases. In addition, in regions where stroke is very common e.g. in East Asia, the incidence of vascular dementia exceeds that of AD [29]. People living with VaD had a 1.26 times larger harzards ratio for all-cause mortality and a 1.33 year shorter survival time after diagnosis than patients with AD, whereas there were no significant differences in age at death [30].

In general, the prevalence of dementia, in particular AD but also VaD is enhancing rapidly in both developing and developed countries. However, there are substantial variations worldwide, e.g. the prevalence of dementia was higher in America and lower in less developed regions of the world, such as Africa and the Middle East, while in eastern European countries it seems to be relatively uniform, lying between the rates of Japan and the US [31]. Attributes to this variations include the lack of methodological uniformity among studies including diagnostic criteria and a lack of autopsy confirmed diagnosis of the underlying neuropathology.

Both subtypes of dementia, AD and VaD, have most risk factors in common [26]. Female sex is an unmodifiable risk factor for AD [3,32,33], while the relationship between female sex and vascular dementia is less clear with studies showing no association at least post-stroke [27]. Only few genetic risk factors are known for vascular dementia [34]. Also, in most cases AD does not have a single genetic cause. However, more than 70 genetic regions have been identified to be associated with AD [35] (Figure 1). One well-known gene, which is a high risk factor in particular in women, is the apolipoprotein E (*APOE*) gene [36]. *APOE* is involved in cholesterol transportation and the metabolism of other fat types in the bloodstream. Problems in this process are thought to contribute to the development of AD, while the involvement of *APOE* in the development of VaD is less obvious [34]. Three rare single-gene variants are known to cause Alzheimer`s disease, including Amyloid

 doi:10.20944/preprints202309.1473.v2

precursor protein (*APP*) on chromosome 21, Presenilin 1 (PSEN1) on chromosome 14 and Presenilin 2 (PEN2) on chromosome 1.

Figure 1. Comparison of genetic risk factors for pathological lesions in AD and VaD. For typical pathological lesions (outermost cycle) of AD and VaD - such as different vascular lesions as well as neurofibrillary tangles (NFTs), Aβ plaques and neuronal/synaptic degeneration- genetic risk factors are indicated (intermediate grey cycle). Where weaker genetic associations with pathological lesions are reported in literature, dotted lines are used connecting the genetic factors with the corresponding pathological lesion(s). .

For both disease entities vascular risk factors are important [37] hinting at a common vascular pathomechanism: Several studies revealed that for a similar burden of Alzheimer`s pathology, clinical symptom manifestation was greater when there was a comorbid vascular disease [26]. There is also strong evidence linking midlife hypertension and diabetes to both, AD and VaD [38]. Midlife cholesterol levels and obesity were associated with later-life dementia [38]. Smoking was a major risk factor for cognitive decline in both, AD and VaD [38–40]. An increased occurrence of vascular risk factors and higher rates of circulatory-associated death have been implicated in the increased mortality risk and reduced life-span survival time in VaD compared to AD, indicating that VaD is part of a general cardiovascular disease [30]. Furthermore, late life depression increased the risk for cognitive decline in both diseases [41] and associations were found providing a plausible mechanistic link between late life depression and several vascular abnormalities. In contrast, a higher cognitive reserve, higher education, social networks, cognitive and physical activity are protective factors preventing cognitive decline [3,38].

To generalize findings on the prevalence and risk factors but also prognosis and mechanisms in AD and VaD, a focus on sociodemographic and health characteristics across ethnoracial groups is required to create an awareness of cohort, survival or inclusion/ exclusion bias. Cohorts based on distinct databases such as the NACC database or the Mayo clinic brain bank may e.g. not even represent the US population in key demographic and health factors which differed by race and ethnicity [42]. Furthermore, different mean population ages may be a source of heterogeneity, even when considering only elderly populations. Standardized age adjustment are not conducted in many epidemiological studies on dementia [42], rising questions e.g. if female sex is still a risk factor when

 doi:10.20944/preprints202309.1473.v2

accounting for age. Besides unequal methodologies and life expectancies, differences in diet and physical activity as all as educational levels may explain most disparities reported for the prevalence of dementia around different regions worldwide. Increased cardiovascular risk factors seem to counterweight the dementia towards a higher prevalence in developed countries [42]. On the other hand, hypertension is a major problem in developing societies correlating to a proportionally high prevalence of VaD. Socioeconomic development increased the prevention, treatment and control of hypertension and with higher life expectance, the prevalence of AD rises, thus increasing the AD/VaD ratio in developed countries [42].

3.2. Clinical Presentation

It is often difficult to distinguish participants diagnosed with AD from those with VaD, based on pure clinical presentation (Table 1) and cognitive performance (Table 2). In AD, symptom progression is somehow reasonably well defined with a relentlessly progressive memory impairment- in particular episodic memory- which converts over months and years to disorientation, personality and judgment dysfunction, speech abnormalities, and apraxias, among other signs of cortical dysfunction [43]. In contrast to AD a well-defined single neuropsychological profile has been challenging to establish for VaD [44]: Clinical symptoms and signs vary depending on the location and size of the stroke lesion(s) and their distribution [45], but generally, deficits in executive functions are most pronounced.

Table 1. depicts typical clinical features for both, AD and VaD. Clinical features were stated according to the *NIA-AA Criteria for AD (https://aaic.alz.org/nia-aa.asp) and the **NINDS-AIREN criteria [58] as well as revised features (proposed by Iadecola et al. [3]) for VaD. **Table 1: Clinical picture of Alzheimer's disease and vascular dementia.**

	AD	VaD
Clinical Picture	• Memory loss* • Progressive decline of cognitive performance • Decline in cognition impacts daily activities • Progressive behavioral abnormalities • Neuropsychiatric symptoms	→ No characteristic symptoms → Heterogeneous clinical picture** • Neurocognitive dysfunction[a] with deficits in attention, information processing and executive function • Behavioral deficits/symptoms[b] • Locomotor abnormalities • Parkinsonian-like gait disorder • Dysarthria • Autonomic dysfunction • Memory variably affected [a] Cognitive decline is on average similar to AD [b] Depression and apathy more prominent in VaD

Abrupt deterioration of cognitive functioning (e.g. when a stroke directly hits important cognitive areas) is described as well as a course of fluctuating intensity of cognitive symptoms or stepwise deterioration [46,47]. Participants with a cerebrovascular cause of cognitive decline tend to reveal a more impaired semantic memory, deficits in attentional functioning, visuospatial and

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perceptual skills and in particular executive dysfunction as most prominent symptoms [46,48,49]. Participants with VaD also tend to show more symptoms of depression, apathy and loss of drive than in AD: In recognition tests for emotions participants with AD outperformed participants with VaD in identifying emotions depicted in the photographs [47]. Table 2 lists differences and similarities when applying neuropsychological tests [50–54]: E.g. while the Mini Mental State Exam (MMSE) provides good results in detecting cognitive decline in Alzheimer`s, the test is quite indifferent for delivering reasonable results for vascular cognitive decline. In contrast, the Montreal Cognitive Assessment (MoCA) has been validated in particular in settings after stroke and suspicion of vascular cognitive impairment. However, if these tests are to be used in clinical settings, they should be applied cautiously and in conjunction with other information, such as medical history, behavioral observations, imaging, and information from relatives, when contributing to a diagnosis [47]**.** Importantly, individuals with VaD may also present with other neurological symptoms such as locomotor abnormalities with gait disturbances and autonomous dysregulation such as bladder dysfunction [55].

Table 2. reveals differences and similarities of neuropsychological test results for diverse aspects of cognition such as memory, language, orientation, attention, perception, concept formation and reasoning as well as executive functions in subjects with AD or VaD. The neuropsychological tests compared in the table are usually part of a general neuropsychological assessment provided in memory clinics during diagnostics. Abbreviations: **-**: not intact; **+**: intact; **o**: no difference between test results in subjects with AD or VaD; **<,>**: worse or better results for subjects with AD or VaD. Abbreviations: **WMS:** Wechsler memory scale; **WAIS**: Wechsler adult intelligence scale. **CERAD:** consortium to establish a registry for Alzheimer's Disease, **MMSE**: mini-mental state examination; **MDRS:** Mattis Dementia Rating Scale; **MoCa**: Montreal-Cognitive-Assessment-Test. **Table 2: Neuropsychological profile of Alzheimer's disease and vascular dementia.**

		AD	VaD
Memory		< [36]	
Dynamics of memory decline		progressive	abrupt or static
Episodic		< [35,39]	
Semantic		> [39]	
Short-term, immediate memory	recognition	-	+
	retrieval	-	-
WMS	immediate recall	o [34]	
	delayed recall	mixed findings	
	working memory	o [34]	
	general memory	o [34]	
Language			
Language verbal fluency (CERAD)	semantic	< [34]	
	phonemic	o [34]	
Boston Naming Testing (CERAD)		< [34]	
WAB	writing	> [53]]	
	block design	> [53]	
Orientation		o [36]	
Attention		o [36]	
Mental control and sustained attention task		≥ [36]	
Visual attention and task switching (Trail making test)		o [36]	

 doi:10.20944/preprints202309.1473.v2

Perception		
Identifying emotions/ facial expression		> [36,39]
Concept formation and reasoning		mixed findings [36,52]
WAIS-R	picture Arrangement	> [53]
	object assembly	> [53]
Executive functioning		> [35,39,40]
Outcome in typical diagnostic tests		
MMSE (CERAD)	Baseline	o [34]
	Follow-up	< [51]
MDRS		> [53]
MoCA - Test sensitivity		< [54]
Clock Drawing Test		o [55]

3.3. Typical Clinical Diagnosis Parameters

While in the 1980s the Aß peptide was identified as well as mutations in the amyloid precursor protein (*APP*) in familiar forms of AD, biomarkers for the diagnosis of AD have been steadily established forming the basis for relatively clear consensus statements for diagnosing AD such as the currently revised National Institute of Aging and the Alzheimer`s Association (NIA-AA) Criteria for the Diagnosis of Alzheimer`s Disease (https://aaic.alz.org/nia-aa.asp, [7]). These criteria have been consistently applied throughout the last years with the three classification systems A (Aß), T (tau) and N (neurodegeneration in MRI or hypometabolism in PET) for the diagnosis of AD [56]. Eight different AT(N) profiles were identified, and individuals were staged based on integrating biomarker profiles and the severity of the clinical impairment. Three new additional categories have been recently added – including I (Inflammation), V (vascular) and S (alpha-synuclein)- to open up biomarkers for AD towards a more differentiated descriptive approach and to include highly relevant co-pathologies.

For VaD the picture is less obvious. Even the term vascular dementia has been controversially discussed for many years as VaD can be caused by a reduced cerebral blood flow supplying the brain which may or may not be associated with a stroke. It can also be caused by a single major stroke strategically destroying important areas for cognitive processing such as the hippocampus or by multiple microstrokes. Subsequently, the term vascular dementia did not fully reflect the entire spectrum of cognitive alterations caused by vascular factors. Thus, the term vascular cognitive impairment (VCI) was proposed [57] and widely adopted. Furthermore, as no clear consensus exists on pathological criteria for VaD, different classification systems such as the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria [58] or the Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) criteria [59] have been developed over time. While the NINDS-AIREN criteria have been proven to be most specific but less sensitive and have been used in most relevant studies [26], the opposite was found for the ADDTC criteria. The latest published Vascular Impairment of Cognition Classification Consensus Study (VICCCS) guidelines [60] require for the diagnosis of vascular cognitive impairment at least "clinically significant deficits in one cognitive domain which are sufficient to cause a severe disruption of activities of daily living and imaging evidence for a cerebrovascular disease". For imaging, a magnetic resonance imaging (MRI) scan is required with identified cerebrovascular lesions. According to the VICCS criteria [3], VaD is classified into four main subtypes (Figure 2): 1) post-stroke dementia, which is defined as dementia disclosing within 6 months after stroke; 2) subcortical ischemic vascular dementia; 3) multi-infarct dementia and 4) mixed dementia. For mixed dementia the predominant case - either AD or VaD- is further specified.

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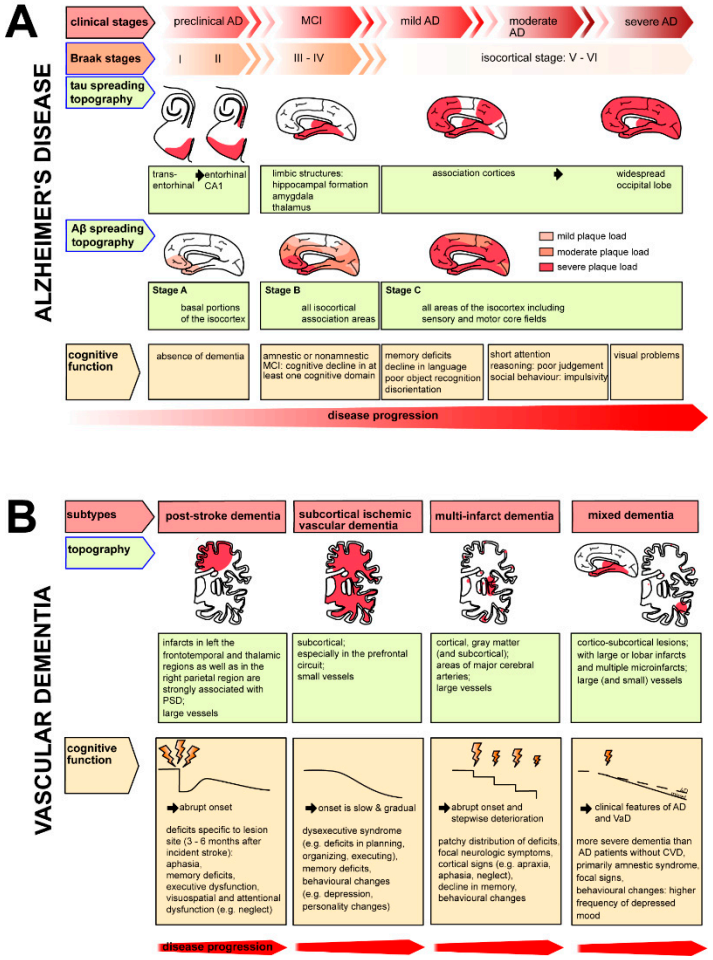

Figure 2. Disease course in Alzheimer's disease versus vascular dementia Clinical courses of disease are compared for AD and VaD and related to typical neuropathological features: AD has a well-defined and predictable disease progression with different disease stages introduced by Braak and Braak [6]. Neurofibrillary tangles (NFTs) appear first in the transentorhinal and entorhinal region of the brain (in stage I and II) and gradually extend to limbic structures (stages III and IV) and association cortices (stages V and VI) while for the Aβ spreading topography the picture is more heterogeneous, only allowing the classification in different stages (A-C). In mild cognitive impairment, the first signs of cognitive decline are apparent in AD patients. Cognition progressively worsens as the disease progresses. In comparison, vascular dementia can be classified into four subtypes (post-stroke dementia (PSD), subcortical ischemic vascular dementia, multi-infarct dementia and mixed dementia) with different lesion types. The clinical course of disease for VaD strongly depends on the number of lesions, lesion type and site of lesion(s) and therefore cognitive decline can be abrupt, slow and gradual or stepwise.

Typical assessment features in MRI for AD include the assessment of general brain atrophy with a focus on medial temporal lobe atrophy and hippocampal atrophy [61,62]. Neuroimaging of VaD should examine also the following [3,60]: 1) General brain atrophy, ventricular size and medial temporal lobe atrophy as well as 2) white matter hyperintensities, 3) infarcts (number, size - stratified for large (>1 cm) or small (3 to 10mm) lesions, location) and 4) hemorrhage (number, size - stratified for large (>1 cm) or small (< 1cm) lesions and location). For the diagnosis of AD further instruments such as Amyloid PET (positron emission tomography) and functional MRI, hold promise to assess structural and functional losses and are on the way in academic centers to become part of the diagnostic routine, in particular in case of difficult diagnosis finding. Furthermore, blood and cerebrospinal biomarkers exists for AD: In addition to decreased Amyloid-beta 1-42 (Aß 1-42) or increased phospho-Tau [63,64], there are new, emerging plasma biomarkers that will make biological

 doi:10.20944/preprints202309.1473.v2

AD diagnosis generally feasible in clinical practice and which perform well to discriminate e.g. AD from other forms of dementia such as frontotemporal dementia and Lewy body dementia [65]. Other markers now mentioned in the revised NIA-AA Criteria include neurogranin as a marker of post-synaptic injury and degeneration while SNAP-25 and GAP-43 are markers of pre-synaptic degeneration and dysfunction. Plasma neurofilament light (NfL) is a marker of large caliber axonal injury that can be measured in cerebrospinal fluid (CSF) or plasma and was used already in various disorders in clinics [66,67]. However, specific molecular biomarkers are missing supporting the diagnosis of VCI.

4. Pathology

4.1. Similar and Distinct Cerebrovascular Features of AD Versus VaD

Atherosclerosis, arteriolosclerosis, cerebral amyloid angiopathy (CAA) and macro- and micro-infarcts increase the likelihood that a person will exhibit dementia symptoms [68,69]. There is growing evidence that cerebrovascular dysfunction and cerebrovascular pathologies may contribute to neurodegeneration also in AD [10–12,70], although the mechanisms of interaction and cause – effects sequences are not fully understood [9]. Vascular pathology is common in elders and increases with advanced age [71]. For instance, 79.9 % of the 4,629 individuals diagnosed with AD based on neuropathological criteria from the NACC database showed vascular pathology [72,73]. Furthermore, 32.2 % from those participants had a cerebrovascular disease [72]. In another study, cerebrovascular lesions coexisted with AD lesions in up to 50 % of cases. In these cases, other cerebrovascular lesions such as lacunes and microinfarcts were also observed [9,72]. Thus, cerebrovascular pathology may simply be co-existing with AD [9] and pure AD may be rare [74]. This is reflected by the Mayo Clinic Brain Bank from 2007 to 2016, in which the majority of AD cases showed other pathologies and comorbidities with advanced age [75]. In the following we are reviewing neuropathological mechanisms leading to endothelial damage, blood brain barrier (BBB) breakdown and hypoperfusion, resulting in haemorrhagic or ischemic lesions, trophic uncoupling in the neurovascular unit and thus accumulation of neurotoxic molecules which in turn leads to neurodegeneration.

4.1.1. Mechanisms of Endothelial Dysfunction

Although it is somewhat common sense that endothelial dysfunction may lead to the insufficient supply of neurons with oxygen and glucose – the mechanisms behind are not well understood and may be multifaceted. A typical pathomechanism resulting in early endothelial dysfunction is athero- and ateriolosclerosis, which as a chronic inflammatory condition affects large and medium-sized arteries [68,76,77] or smaller vessels [68]. Different risk factors such as dyslipidemia, arterial hypertension and diabetes mellitus are associated with the emergence of atherosclerosis [76,78]. Formation of atherosclerotic plaques and their calcification aggravates fibrosis and degenerative processes of vessel walls, inducing infarcts due to thrombosis or embolism. Beach et al., [79] reported that in particular the atherosclerosis of the Circle of Willis was more severe in subjects with AD and VaD than in control subjects, while it was equivalent between control subjects and subjects with non-AD dementias. Severe circle of Willis atherosclerosis was even more common in VaD. With an increasing severity of atherosclerosis, the odds ratios (OR) for the diagnoses of both, AD and VaD, are pronounced, also for neuritic plaque density and higher Braak neurofibrillary tangle stages in the case of AD. A similar result was found in a populated-based cohort study in which 678 volunteers developed dementia (476 were diagnosed with AD, 52 with mixed pathology, and 78 with VaD). Atherosclerosis- this time predominantly at the carotid artery- was associated with an increased risk for dementia [80].

Atherosclerosis very often coexists with small vessel disease (SVD), an umbrella term that includes various pathological findings, including small infarcts, microscopic infarcts, CAA and arteriolosclerosis [3]. Together, atherosclerosis and SVD are among the most frequently associated vessel pathologies found in VaD: Changes of intracranial small vessels lead to Binswanger's disease

 doi:10.20944/preprints202309.1473.v2

or subcortical ischemic vascular dementia [26,29,55,81]. In addition, atherosclerosis starting already in midlife was rather associated with the development of VaD and SVD [82] than with the development of AD. However, in the context of AD an association of the *APOE*4 allele and atherosclerosis is discussed, although strong evidence is still missing [79,83].

Besides atherosclerosis, cerebral amyloid angiopathy (CAA) is common in older individuals and the most common cause of intracerebral hemorrhage, contributing to cognitive decline [43,84]. The pathology leading to cerebrovascular dysfunction is characterized by the deposition of amyloid, mainly Aβ, in the media and adventitia of small and mid-sized cerebral and leptomeningeal vessels, accompanied by degeneration of smooth muscle cells (SMC) [85–87]. Subsequently, CAA leads to a disrupted cerebrovascular architecture and BBB damage [73,81,85]. Furthermore, CAA causes not only hemorrhages, including microbleeds, but also capillary occlusion and blood flow disturbances leading to infarcts and white matter lesions resulting from hypoperfusion and dysfunctional vascular autoregulation [81,85,86,88].

Clinically, CAA manifests in 5 - 20 % of all cases with lobar intracerebral hemorrhages [86], indicating the strong connection between CAA and cerebrovascular lesions. CAA is found in both, individuals with AD and VaD. While the prevalence of CAA in VaD is still unclear [55], the cerebral vasculature of individuals with AD is very often affected by CAA, occurring in over 90 % of the cases [9,43,85,88]. However, recent findings [89] indicate, that pathological vascular alterations are not only a consequence of Aβ deposition, but that vice versa, impaired cerebral vasculature may contribute to the accumulation of Aβ plaques: In mouse models of Aβ pathology, experimental manipulation inducing deficient endothelial cells or pericytes and an impaired BBB augmented Aβ plaque load [89]. Therefore, disrupted Aβ clearance through the cerebrovascular system may be a pivotal process in the development of AD.

CAA is most frequently and severely affecting the occipital lobe, which might be due to a higher number of tortuous occipital vessels, leading to decreased perivascular clearance [86,90,91]. CAA was also frequently located in the frontal, temporal, or parietal lobes [90–94]. In all regions, the leptomeningeal vessels seem to be in particular susceptible for CAA [91]. A study by Haglund et al. [95] described in this context more amyloid-positive vessels in the leptomeninges and in the cortex in participants with mixed dementia pathology than in individuals with a AD diagnosis only. For VaD, a preferentially affected region could not be identified in the literature so far.

Genes connected to AD and cerebrovascular lesions are *APOE* e4, *APOE* e2, mutations in CR1 and *APP* gene polymorphism. *APOE* e4 is not only an established susceptibility gene for AD, but is also associated with an increased risk of CAA, which emphasizes the link between AD and CAA [9,26,85,86,96–98]. For VaD, such a clear link does not exist with inconsistent reports of an association between *APOE* e4 and an increased risk for CAA in VaD [99]. However, *APOE* e2 is described to be a risk factor for CAA-related hemorrhage [85,88,96,100] and thus might intercept with vascular dementia.

Furthermore, mutations in presenilin 1 or presenilin 2 genes are associated with familial AD and severe CAA [88]. According to Pandey et al., [101], Presenilin 1 allele 1 is susceptible to degenerative dementia, but not to VaD. In addition, mutations in the *APP* gene were identified with familial forms of AD and with sporadic CAA, as well as familial (or hereditary forms of) Aß and non-Aß-CAA [9,90,98,102]. Hereditary forms of CAA with mutations in the *APP* gene do also contribute, although not consistently, to cerebral vasculopathies [90,98] and are characterized by multiple hemorrhages and infarcts in addition to severe amyloid depositions in the walls of vessels leading to VCI or VaD [55,90,98].

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4.1.2. Mechanisms of Blood Brain Barrier (BBB) Breakdown

An association of brain cells, including brain endothelial cells, mural cells (pericytes and vascular smoot muscle cells), astrocytes, neurons, microglia and a basement membrane form the so-called neurovascular unit and enable BBB function [103]. Cerebral endothelial cells are connected via tight junction and adherens junctions, creating a barrier [9,73]. While an intact blood brain barrier is crucial for the homeostasis of the central nervous system (CNS) and protects from toxins and pathogens, endothelial dysfunction and alterations in BBB permeability probably precede several pathological alterations, thus playing a major role in the pathology of different neurovascular diseases [104].

BBB dysfunction was found both, in individuals with AD and VaD [97][105]. Moreover, BBB breakdown seems to take place early in the course of both diseases, in particular affecting the hippocampus in AD [106]. It was thus even suggested that BBB dysfunction precedes hippocampal atrophy seen later in AD. A recently published review on dysfunctional BBB in AD [107] shows, that BBB breakdown was detectable early in the course of AD on MRI. In addition to the hippocampus, disruption of BBB in early AD was detectable on dynamic contrast-enhanced MRI (DCE-MRI) also in other grey and white matter regions associated with cognitive decline and dementia [108,109].

A common explanation for endothelial dysfunction may be endothelial damage – induced by a figurative vicious cycle of hypoperfusion and oxidative stress- which in turn results in reduced resting cerebral blood flow (CBF) in the marginally perfused white matter and in an altered BBB [9]. As a result, hypoxia and additional oxidative stress induce inflammatory pathways and altogether lead to injured oligodendrocytes, demyelination and trophic uncoupling in the neurovascular unit [9,110,111]. Damage to the neurovascular unit- of any of the components - vice versa- contributes to impaired cerebrovascular cells (Figure 3). Supporting this, CBF reduction in individuals with early AD correlated with an increased BBB leakage rate [112–114].

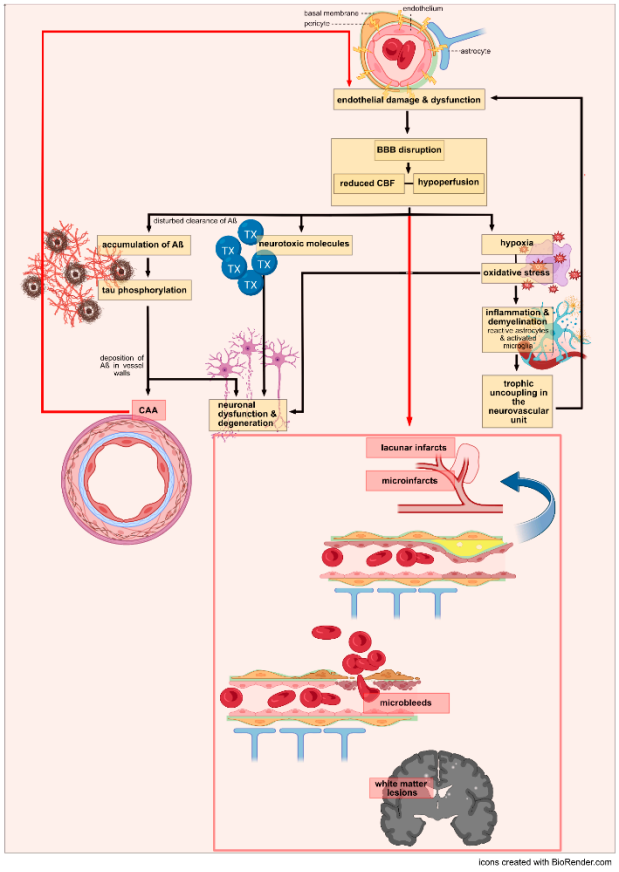

Figure 3. Common pathomechanisms in Alzheimer`s and vascular dementia:Cerebral endothelium, astrocytes and pericytes are an essential part of the formation and function of the blood-brain barrier

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(BBB). Endothelial damage leads to BBB breakdown and reduced cerebral blood flow (CBF), which induce on the one hand oxidative stress, inflammation and demyelination and thus trophic uncoupling in the neurovascular unit and on the other hand accumulation of neurotoxic molecules and Aß through impaired clearance, leading to neurodegeneration. Trophic uncoupling in the neurovascular units as well as deposition of Aß in the media and adventitia of small and mid-sized cerebral and leptomeningeal vessels, results in cerebral amyloid angiopathy (CAA) and aggravates vascular dysfunction. Disruption in the endothelial function, BBB and thus in the CBF and perfusion (resulting in reduced CBF and hypoperfusion) cause different types of hemorrhagic and ischemic lesions such as lacunar infarcts, microinfarcts, microbleeds and white matter lesions (summarized in the red box).

In particular the role of astrocytes and microglia has recently gained more attention as BBB integrity is dependent on the structural coverage of astrocytes. Astrocytes change their morphology with decreased cell volume, cell surface and process numbers (atrophic features) along with end feet retraction and detachment from blood vessels accompanying BBB breakdown [115–117]. In contrast, "reactive" astrocytes with hypertrophy, proliferation, and augmented expression of intermediate filaments have been found near Aβ plaques in both, post-mortem human brain tissue and animal models [115]. Although a priori considered as protective reaction and relatively early seen even before the appearance of Aβ deposits [118], this astrocyte activation could directly contribute to the defective clearance of Aβ. Astrogliosis results in downregulation of key proteins such as astrocytic GLUT1, lactate [119] and ABC (ATP-binding cassette) transporters for xenobiotics and endogenous metabolites [120] as well as Aquaporin 4 and Connexin 43(Cx43), indicating a loss of astrocytic polarity and leading to edema and swollen end feet, along with increased matrix metalloprotrease (MMP) release and decreased dystroglycan levels [121]. These mechanisms induce astrocyte detachment in the capillary basement membrane affecting BBB integrity.

In addition, astrocytes are the main source of Apolipoprotein E (ApoE). ApoE has been shown to impact the integrity of the BBB, and, in humans, the *APOE4* allele of the gene (a major risk factor for AD but also detected in VaD [78]) is reported to lead to a leaky blood–brain barrier [122] by activating a pro-inflammatory pathway resulting in neuronal uptake of blood-derived neurotoxic proteins [113,123–125]. Carriers of *APOE*4 allele were distinguishable from non-carriers by BBB breakdown in the hippocampus and medial temporal lobe. These findings were even more severe in *APOE*4 carriers with cognitive impairment [125] and support the two-hit hypothesis which is discussed for the development of AD [89,108]: According to the hypothesis, cerebrovascular damage is the initial insult, the so-called "first hit". Damage to brain microcirculation leads to a dysfunctional BBB and diminished brain perfusion, which in turn induces hypoperfusion and accumulation of neurotoxic molecules. This mediates neuronal dysfunction and disturbed Aß-clearance and thus Aß accumulation in the brain (second hit). Increased levels of Aß amplify neuronal dysfunction and accelerate neurodegeneration [73,89,126].

Furthermore, misfolded and aggregated proteins bind to pattern recognition receptors on micro- and astroglia and trigger an innate immune response with release of pro-inflammatory cytokines and other immunological modulators promoting AD progression [127–131]. In this respect, several candidate genes, which have been identified as risk factors for AD, encode for proteins that regulate microglial and astroglial clearance of misfolded proteins and other inflammatory responses, e.g. the ABC transporter A7 which mediates the phagocytic clearance of Aβ in the brain [131–133], and TREM2 which is involved in microglia-mediated clearance of tau. Thus, these pathophysiological pathways may deliver promising treatment targets in AD [134,135].

Extensive literature also discusses other molecular mechanisms underlying a dysfunctional BBB: P-glycoprotein, for example, is an efflux pump, which is expressed at endothelial cells of the BBB and is involved in the transportation of Aß [136,137]. It was shown, that vessels with high P-glykoprotein expression revealed no Aß-accumulation in their walls, suggesting, that impaired clearance of P-glycoprotein leads to Aß accumulation, which increases the risk for cerebral amyloid angiopathy (CAA) and AD [136]. Activity of P-glycoprotein could be assessed in vivo and was found to be

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reduced in frontal, parietal, temporal, and occipital cortices as well as in anterior and posterior cingulate cortex in participants with AD [137], while only the parietotemporal, frontal, and posterior cingulate cortices and hippocampus were affected in participants with mild AD [138]. Altered P-glykoprotein levels were also identified in several animal models targeting neurovascular risk factors such as diabetes mellitus and hypertension: Maeng et al., [139] investigated the clearance of cyclosporin A via P-glykoprotein in streptozotocin-induced diabetic rats in vivo. The clearance of cyclosporin A was reduced and was associated with an increased mRNA and protein level of P-glycoprotein [139]. Another study detected an increased expression of P-glycoprotein in hippocampal vessels with impaired BBB of stroke-prone spontaneously hypertensive rats (SHRSP) [140]. The increased levels of P-glykoprotein could be a compensatory strategy in VaD or may even reflect a different molecular mechanism at the BBB level in the pathology of AD and VaD, as in AD disappearing P-glycoprotein levels were measured in smooth muscle cell layers of arterioles were Aß was deposited. However, at the same time P-glycoprotein levels were increased in capillaries. Thus, P-glycoprotein seems to serve as a gatekeeper to the BBB with even a suspected neuroprotective role in AD [141] while the same was not reported for VaD.

Other molecular factors related to the BBB which were differently expressed in individuals with VaD and Alzheimer`s include plasma cyclophilin A [142] or LRP1, a major Aß clearance receptor [28].

4.1.3. Mechanisms of Altered Cerebral Blood Flow

Alterations in cerebral blood flow have been linked to age-related cognitive impairment since the time of Alois Alzheimer, best known for identifying the condition now called Alzheimer`s disease. Alzheimer proposed that stiffening of arteries would impair the ability of cerebral blood vessels to relax and adjust the delivery of blood to the metabolic needs of the brain, causing hypoperfusion, neuronal death and dementia [3]. This concept prevailed for many years, till measurements of cerebral blood flow demonstrated that cerebral blood vessels were able to increase cerebral blood flow also in cognitively impaired individuals [143]. However, resting cerebral blood flow (rCBF) was shown to be reduced in individuals with hypertension in prefrontal, anterior cingulate and occipital areas over time [144]. Thus, reduced CBF might represent an early pathological process in both forms of dementia (see [113,145,146]).

In particular the deep white matter is vulnerable to decreased CBF [9], alongside other susceptible brain regions such as the basal ganglia and the hippocampus [147]. Individuals with AD and with subcortical ischemic vascular dementia (SIVD) showed reductions of the CBF in the same regions- the frontal, parietal and the temporal cortex [148–151].

However, reductions of the CBF tend to be more prominent in the posterior brain areas in AD [152]. Specifically, CBF was reduced in posterior cingulate and precuneus cortex in mild cognitive impairment (MCI), whereas AD was associated with more global and severe CBF reduction [151,153] and the involvement of other areas such as the bilateral parietotemporal, frontal and occipital cortex, parahippocampal gyrus, hippocampus and entorhinal cortex [151].

In contrast, reduction of CBF tends to be anterior-dominant in VaD [152], preferentially involving the frontal lobe [154,155]. Compared to normal controls a reduced CBF has also been reported in the right thalamus, left caudate nucleus and in the cingulate, bilateral superior temporal and left ventral subcallosal gyri in subcortical VaD [156]. In line with the described anterior-dominant lower CBF perfusion, resting CBF (rCBF) was reduced in the frontal and temporal white matter in participants with VaD [150].

Furthermore, Aβ, the major pathogenetic marker for Alzheimer`s disease, is discussed of having a vascular effect in reducing cerebral blood flow alongside endothelial dysfunction [9]. Also *APOE*4 is associated with BBB disruption and reduced CBF [113,123–125,151]. Several studies showed greater reduction of CBF in carriers of *APOE*4 compared to non-carriers [157–160]. Differences were in particular observed in the frontal, parietal and temporal area [158] and in mid-life individuals (aged 40 – 59) carrying the *APOE*4 allele [160]. Other authors [71] also discussed a dysfunction of the cholinergic system, which is reported for both, AD as well as VaD [102,161,162], causing a reduction of the CBF.

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Concluding from these findings, parameters of CBF and phenomena of local reduction- e.g. preferentially anterior in VaD and posterior in AD- as well as BBB components such as P-glycoprotein might be useful early markers for diagnosing preclinical AD and VaD [151,160] .

4.1.4. Cerebrovascular Lesions

Damaged blood vessels, a dysfunctional blood brain barrier and an altered cerebral blood flow ultimately lead to cerebrovascular lesions.

Micobleeds e.g. result from blood leakage and extravasation into the perivascular space [9,73,153] and are visualized as small, dot-like hypotense abnormalities in the MRI and are associated with hypertension and white matter disease [9,163]. Microbleeds are observed in both, AD and VaD, however with different frequencies. While the prevalence of microbleeds ranges from 35% to 85% in VaD [55,163], microbleeds in AD are usually detected at lower percentages using MR imaging. For example, 18 % of participants with AD exhibited microbleeds compared to 65 % of participants with VaD [164].

The location of microbleeds is related to their etiology: a hypertensive vasculopathy presumably leads to deep and infratentorial microbleeds, while CAA most likely plays a role in lobar microbleeds [163,165]. According to Yates et al. [166], the majority of microbleeds in AD might be caused by CAA and thus tend to appear in posterior cortical regions, especially in the occipital lobe [73,165–168]. Pettersen et al. [168] for example, reported a lobar predominance of microbleeds in 92 % of subjects with AD on T2-weighted and proton density-weighted scans. 57 % of these microbleeds were detected in the occipital lobe. In contrast, another study observed an anterior-posterior decreasing gradient of cortical microbleeds in individuals with AD, who showed more cortical microbleeds in the superior frontal, inferior temporal, the rectus and the cinguli gyrus, and in the insular cortex compared to controls [169]. In hereditary VaD, such as Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (*CADASIL*), microbleeds are scattered throughout the brain with a preference for subcortical lesions, white matter, thalamus and brainstem – but also lobar regions [163,170]. Furthermore, comparing cortical microbleeds in participants with VaD versus individuals with mixed dementia, revealed a predominance of microbleeds located in the frontal lobe and the cerebellum of subjects with VaD [171].

Looking for genetic risk factors for microbleeds, the *APOE* gene again appears as a major player associated with sporadic microbleeds. Both alleles, *APOE* e2 and *APOE* e4, have each been reported to be related to lobar microbleeds [166]. Maxwell et al., [172] also observed an association of *APOE* e4 with deep microbleeds, while another study found only an association of *APOE* e4 with lobar microbleeds, but not with deep and infratentorial ones [173]. As *CADASIL* presents with microbleeds and is subject to the mutation of *NOTCH*3, mutation of *NOTCH*3 can be also considered as a genetic risk factor for microbleeds.

Ischemic counterparts of microbleeds are **microinfarcts** appearing as small cystic or gliotic, pale lesions, which occur throughout the brain. They induce neuronal loss and show in the acute stage an inflammatory response [9,55,174]. The size of microinfarcts is often described to be not visible to the eye or only upon microscopy indicating the limited use of the MRI for their detection. Only ultra-high field strength clinical MR scanners might detect microinfarcts in individuals [174]. Microinfarcts are in particular found in SVD. But they can also originate from embolic events due to atherosclerotic plaques [174,175]. Microinfarcts (especially multiple cortical microinfarcts) are common, their number usually increases with age [176] and they are detected in particular in VaD (62 %), but also in AD (43 %) or mixed pathology (AD with cerebrovascular disease; 33%). Microinfarcts can be localized cortically and subcortically [177]. In particular, for subjects with AD, microinfarcts are found cortically, in close proximity to CAA [178], indicating that cortical microinfarcts are probably caused by amyloid angiopathy. Moreover, these cortical microinfarcts are predominantly located in the occipital lobe in AD [178]. However, some studies also found cortical microinfarcts in individuals with AD in the motor cortex with existing motor impairment [177]. For VaD cortical microinfarcts

 doi:10.20944/preprints202309.1473.v2

were reported in the frontal lobe and cerebellum with cerebral arteriolosclerosis thought to be the main cause [171].

Furthermore, **subcortical (lacunar) infarcts** are determining pathological features of SVD [29,179], and thus also for VaD. Lacunar infarcts are small (1-15 mm), discrete and often multiple and bilateral irregular lesions [55,180], which are located in deep parts of the brain, but not in the cerebral or cerebellar cortices [180]. These kinds of lesions are thought to be an age-related neurovascular disorder [181], originating either from vessel occlusion related to SVD or from embolic events [81]. Around 68 % of the cerebrovascular lesions seen in pure VaD (VaD without AD pathology) are subcortical lacunar infarcts [182]. Moreover, it is reported, that lacunar infarcts are identified in 25 % of all ischemic strokes [181]. Lacunar infarcts are also the most common feature in more than 50 % of elderly subjects with ischemic VaD [55]. Lacunar infarcts are part of the cerebrovascular pathology detectable in AD [182], having been associated with the same risk factors as in AD, among which advancing age is particularly noteworthy [181]. In the study of Snowdon et al., [183], 39 % (n=24) of the 61 participants with AD showed at least one infarct. Considering the localization of lacunar infarcts, for both disease entities, AD and VaD, lacunar infarcts typically occur in the basal ganglia, thalamus, and white matter (see table 10 in Jellinger [85] and Tikka et al., [184]). However, for participants with AD and severe cerebrovascular disease (mixed dementia) larger and more lobar infarcts are found than small subcortical lacunar infarcts [182]. In VaD, lacunar infarcts predominate in the deep white matter [185] and/ or subcortical brain areas (in particular the putamen) and are associated with intracerebral hemorrhage [9,26,55]. Especially in *CADASIL*, lacunar infarcts are described as typical features and of diagnostic importance [9,26,186]. T2-weighted changes and lacunar infarcts in the MRI located in the external capsule and the anterior part of the temporal lobe are highly suggestive of *CADASIL [187]* .

Further cerebrovascular lesions include **white matter rarefaction (Leukoaraiosis)** representing abnormal modifications of the white matter, detectable as hyperintensities in the MR and including demyelination, axon loss, astrogliosis and microglia activation [81]. White matter rarefaction is associated with vascular risk factors [188,189] and was found to be related to CAA and SVD [188]. Although the exact neuropathological mechanisms for the development of white matter rarefaction remain obscure, ischemia, a dysfunctional blood brain barrier (BBB) and endothelial dysfunction are being discussed. While white matter rarefaction is a hallmark feature of VaD [55,190], these type of lesions are also found in AD. Englund [191] could detect white matter lesions in 33 of 60 (55 %) participants with AD. In addition, the review of van Gijn [189] reported an occurrence of white matter lesions in 25- 60% of volunteers with AD. Moreover, white matter lesions were more frequently found in late-onset AD and in AD without parietal predominance [192]. In an imaging study, comparing white matter lesions in VaD and AD, all subjects with VaD had white matter changes, while in AD only a small proportion revealed these features, leading to the author's assumption, that white matter lesions might be a useful diagnostic tool for differentiation [190].

White matter lesions can be diffusely distributed in the brain or very focal in both disease entities, AD as well as VaD. In subjects with AD, white matter lesions were predominantly distributed posterior [166]. Others [191] however, also reported white matter lesions in the frontal deep white matter. White matter degeneration was situated next to advanced cortical degeneration in the temporal lobes. Thus, it is suggested that white matter lesions in AD are a possible consequence of Wallerian degeneration of nerve fibers caused by neuronal loss [193]. Similar mechanisms can be true for VaD, however on a much higher level [194].

Genetically, a link between AD and VaD may exist for ischemic lesions. In a genome-wide association study [195] evidence for a shared genetic contribution between AD and small vessel stroke was found. Polymorphism of homozygous methylene-tetrahydrofolate reductase *(MTHFR 677TT)* and of angiotensin converting enzyme *(ACE) D/D* seemed to contribute to white matter lesions in AD and VaD [196]: Elevated levels of homocysteine, which cause endothelial dysfunction and are a known risk factor for VaD, can be associated with the *MTHFR 677TT* variant, whereas *ACE D/D* polymorphism is presumably interfering with the vaso-regulatory system [197]. Both genetic defects can therefore lead to chronic hypoperfusion of the white matter, which in turn is most likely

 doi:10.20944/preprints202309.1473.v2

causing white matter lesions [197]. Furthermore, for VaD three hereditary small vessel diseases (SVD) are known, typically leading to lacunar infarcts and white matter rarefaction: *CADASIL*, *CARASIL* [184,198] and the *COL*4 (Clinical spectrum of type IV collagen) disorder. As already described in the chapter above, *CADASIL* is caused by the defective gene *NOTCH*3, while *CARASIL* is a rare and recessively inherited disease [184], in which mutation of the gene *HTRA*1 (high-temperature requirement A serine peptidase 1) was identified [9,184,199]. Characteristic for *CADASIL* are white matter hyperintensities in the temporo-polar region and capsula externa as well as a periventricular spotty white matter rarefaction [184,198]. MRI findings in *CARASIL* are mostly similar to those in *CADASIL*. However, white matter lesions in *CARASIL* appeared to develop more homogenously than in *CADASIL* [184].The *COL*4 disorder is another rare condition that presents with multiple lacunar infarcts in the white matter and the pons and is caused by mutations in the *COL4A1* gene, encoding the type IV collagen alpha 1 chain [9,55].

4.2. Similar and Diverse Neuronal Features of AD Versus VaD

4.2.1. Brain Areas Differently Affected in AD and VaD

Macroscopical Changes

Dementia is related to neuronal loss that leads to brain atrophy years before the manifestation of clinical symptoms [200]. Despite the observation of the relatively ordered spread of neurofibrillary tangles (NFTs) leading to neuropathological classification of different disease stages [161,201] and associations found between NFT deposition and brain atrophy, there is increasing evidence of heterogeneous patterns of brain atrophy in individuals with AD. However, at least in the dominantly inherited form of AD the pattern and degree of individual brain atrophy can predict dementia onset [202] and novel statistical models and machine learning [203] can help to identify and cluster patterns of regional brain atrophy [204]. It is also established that serial atrophy rates are significantly higher in AD compared with similarly aged controls and subjects with VaD [205]. In AD, there is a generalized atrophy with focal changes in the temporal lobe, especially the hippocampus. Cortical thinning, which is significantly affecting the hippocampus, leads to a dilatation of the adjacent temporal horn of the lateral ventricle and together with medial temporal lobe atrophy it can be interpreted as a possible early pathomorphological sign of AD on MRI [206,207]. But compared to the typical medial temporal lobe atrophy, atrophy of the entorhinal cortex was found to have a higher diagnostic accuracy [208]. Other important regions showing cortical atrophy are the parahippocampal and the superior frontal gyrus. Very little cortical atrophy occurs in the occipital lobe and cingulate gyrus [209,210].

Brain atrophy is also evident in VaD. An investigation of brain atrophy on serial MRI in participants with Lewy Body dementia, AD and VaD, revealed higher rates of brain atrophy in subjects with dementia compared to control subjects, without any significant differences between the three dementia groups [210]. Atrophy in VaD is generalized and similar to AD also located in the medial temporal lobe [26,55]. Moreover, the hippocampus is also affected in VaD, in which van de Pol [211] could detect a similar reduction in the volume (11.6 %) compared to AD (16.6 %). Also, the pattern of hippocampal atrophy was similar in both disease entities [212]. Another study indicated that both, hippocampal and cortical atrophy, correlated best with subcortical vascular dementia and AD. The characteristic feature of *CADASIL* white matter rarefaction, but also the disease itself, were associated with focal cortical thinning [213,214]. In the study by Seo et al., [214] deep white matter hyperintensities were associated with cortical thinning in the frontal and lingual gyrus. In addition, brain atrophy in *CADASIL* was associated with the volume of lacunar lesions and progressed three times more rapidly compared to normal aging [198]. Cortical thinning in subcortical vascular dementia was most evident in the frontal regions (bilateral inferior frontal, superior temporal gyri and right medial frontal and orbitofrontal lobes) and more prominent than in individuals with AD, where the right medial temporal region was significantly more affected [215].

 doi:10.20944/preprints202309.1473.v2

Furthermore, areas vulnerable for micro-infarcts, neuropathological changes related to SVD and consecutive atrophy in VaD are so called watershed brain regions [216,217]. These regions are located at the most distal areas between arterial territories - e.g. the anterior and middle cerebral artery (anterior watershed region) or the middle and posterior cerebral artery (posterior watershed region). Interestingly, linear regression models revealed an increase in the severity of arteriolosclerosis in posterior watershed regions which was associated with a higher burden of tau pathology, but not with Aß [218].

Changes on Cellular and Subcellular Structures

Both disease entities, AD and VaD, present with neuronal and synaptic loss [207], including dysfunctional neurotransmitter systems [43] (Table 3). Areas in particular affected by neuronal and synaptic loss for both forms of dementia are as already mentioned above, the hippocampus, the dorsolateral prefrontal cortex and the cholinergic nucleus basalis Meynert [212,219–221]. The hippocampus is known for its high degree of neuroplasticity. But this feature might also be the reason for the pronounced vulnerability of the hippocampus to ischemia and chronic stress [222]. Damage to the hippocampus is most evident in CA1 hippocampal neurons, in which a brief episode of cerebral ischemia already results in cell death [222]. Furthermore, regional differences in antioxidants and inflammatory reactions may contribute to the vulnerability of the CA1 region [222]. Hippocampal sclerosis (HS) is a pathologic term used to describe severe loss of neurons and reactive gliosis without cystic cavitation in the CA1 sector of the hippocampus [223]. In autopsy series, HS may be found without significant other pathology (2%–4% of cases), but it occurs frequently in combination with other vascular and neurodegenerative disorders (12%–20% of cases [224]).

Table 3. summarizes similar and diverse neuronal pathological features in AD versus VaD. Abbreviations: **AD**: Alzheimer's disease; **VaD**: vascular dementia; **ADCI**: Alzheimer's disease related cognitive impairment; **CVD**: cerebrovascular disease.**Table 3: AD-like pathology.**

Alzheimer' s versus vascular dementia				
pathological features		similarities	differences	
			AD	VaD
atrophy	general	-	• typical appearance: atrophy with widened sulci and narrowed gyri [31,169,201] • atrophy most pronounced in the association areas [31,200,201]	• global cerebral atrophy [59,73] • focal cortical thinning specifically for *CADASIL* [208,214]
	temporal lobe	• medial temporal lobe [31,59,73,200,201] • hippocampus (CA1) [59,201]	• earliest lesion in the medial temporal lobe [200,201] • atrophy of the entorhinal cortex [202] and the parahippocampal gyrus [203,204] • dilatated temporal horn of the lateral ventricles [200,201]	-
	frontal lobe	-	• superior frontal gyrus atrophy [203,204]	• cortical thinning mostly evident in the frontal regions compared to AD [215]

 doi:10.20944/preprints202309.1473.v2

	occipital lobe	-	• minor occipital atrophy [203,204]	-
	cingulate gyrus	-	• minor atrophy in the cingulate gyrus [203,204]	-
neuronal & synaptic loss	location/ systems	neuronal loss in [31]: • the hippocampus (CA1) [207,216] • the nucleus basalis Meynert [217] • layer III and V in the dorsolateral prefrontal cortex 217]	neuronal system degeneration: • spreads from entorhinal cortex to the hippocampus, temporal cortex, frontoparietal cortex and subcortical nuclei [201,229,230] • affects subcortical areas: nucleus basalis of Meynert, locus coeruleus, substantia nigra pars compacta, dorsal raphe nucleus [200,217,219–221,223,227]	neuronal system degeneration: • minute neuronal loss found in all brain regions [17] • *CADASIL*: neuronal loss in layer III and V of the neocortex [228]
	location/ systems genetics	synaptic loss [31]: • disruption in glutamatergic system [237,238] • disruption in serotoninergic system [128,227,239] • impaired cholinergic neurotransmission [17,127,128,240]	synaptic system: • AD and mixed dementia with greater deficits in the cholinergic system in the temporal cortex [240]	synaptic system: • decreased serotonin metabolism in hypothalamus and caudate nucleus [128] • impaired cholinergic system in the basal forebrain [17] • *CADASIL*: severe cholinergic deficits in frontal and temporal cortices][240]
		• *APOE* 4 [242] • *APP* [242]	presenilin 1 and 2 genes [242]	• *CADASIL* [228,240] • *ERBB*3: was downregulated in animal model [243]
	subtypes	• neuronal loss associated with the severity of CAA [269]	-	-
	tau & ß amyloid	• interaction between vascular pathology and Aß and tau pathology [16,248,252]	-	-
	tau & ß amyloid	• concurrent Aß pathology in VaD [16,248,252]	• so-called “hallmark” lesions[31,35,131,201]	

 doi:10.20944/preprints202309.1473.v2

		• especially Aß-42 was found to be accumulated in both diseases [249]	• greater neuritic plaque score[64] • greater Braak stage[64] • 9-fold higher mean tangle density[48] • spreading pattern in ADCI: appears first in the parietal and frontotemporal regions [248] • t-tau protein level highest in the frontal lobe [48] • p-tau levels increased in the temporal lobes [48]	• spreading pattern: appears first in the parietal and occipital regions [248] • selective loss of t-tau protein in the temporal and frontal lobe [48]
		composition in the cerebrospinal fluid (CSF) [49]: • decreased Aß1-42 levels • increased tau-levels in probable AD, AD with CVD and probable VaD	• p-tau increased [49] • percentage of Aß1-42 decreased [49]	-

AD: Alzheimer's disease; **VaD**: vascular dementia; **ADCI**: Alzheimer's disease related cognitive impairment; **CVD**: cerebrovascular disease.

Besides the hippocampus, reduced pyramidal cell volumes were found in layer III and layer V of the dorsolateral prefrontal cortex in VaD, mixed dementia and AD compared to individuals without dementia symptoms [221]. Furthermore, neuron numbers and nucleolar volumes in the cholinergic nucleus basalis Meynert were decreased in pure AD and in mixed dementia (AD and VaD), although pure multi-infarct dementia showed, on average, no significant changes [220,225].

For AD, region-specific neuronal degeneration was also reported in other subcortical areas such as the locus coeruleus, substantia nigra pars compacta, and the dorsal raphe nucleus [206,226,227]. The suggestion arose that of these subcortical areas, the locus coeruleus is the site where the first pathological alterations in AD commence [227]. It was shown that intraneuronal lesions associated with AD occur early, affecting the locus coaeruleus and thus the noradrenergic system [228]. Studies reported a neuronal loss of 60% in the locus coaeruleus in AD compared to controls [229]. In the serotoninergic system, alterations have been initially described particularly in the temporal and frontal cortex. Further studies observed a substantial loss of serotonin type 1 and 2 receptors in the amygdala, neocortex and hippocampus [230].

In contrast to AD, microinfarcts with neuronal loss can be found in essentially all brain areas in VaD [71]. However, for CADASIL neuronal apoptosis was specifically observed in layers III and V of the neocortex. Neuronal loss correlated with the extent of ischemic lesions and axonal damage in the underlying white matter [231].

On the subcellular level, synaptic loss is a characteristic pathomorphological feature that precedes neuronal loss, as in particular shown for AD [232]. The pattern of this neuronal and synaptic degeneration in AD matches with that of the appearance of neurofibrillary tangles and plaques [207]. Neurodegeneration starts in layer II of the entorhinal cortex and spreads into the hippocampus, temporal cortex, frontoparietal cortex and subcortical nuclei [232,233]. Furthermore, microglia activation has been found to play a considerable role in neuroinflammation spreading fastest along highly connected synaptic pathways. This trans-synaptic propagation was in many ways similar as the trans-synaptic propagation of tau occurring through anatomically connected synapsis [234].

 doi:10.20944/preprints202309.1473.v2

These results could be further confirmed in humans using translocator protein (TSPO) PET imaging [235,236]

Considering dysfunctional neurotransmitter systems, in AD (and for some cases also in VaD) in particular the glutamatergic [237,238], the serotoninergic [161,239] and the cholinergic systems are impaired [71,102,161]. For VaD, neurochemical studies found abnormalities in the cholinergic transmitter system in the basal forebrain [71]. Dysfunction of the cholinergic system was also found in the temporal cortex, in which choline acetyltransferase activity revealed a more decreased activity in participants with AD and mixed dementia than in controls and individuals with "pure" VaD [240]. Furthermore, *CADASIL* exhibits especially severe cholinergic deficits in the frontal and temporal cortices [241]. And even for the serotoninergic system a decreased serotonin metabolism was identified in subjects with VaD in the hypothalamus and caudate nucleus [161].

4.2.2. Genetic and Cell-Cycle Related Changes Involved in Neuronal Loss and Brain Atrophy

Some genetic risk factors for AD (*APP*, *APOE*4, presenilin 1 and 2) cause accumulation of Aß which subsequently leads to neuronal and glial pathology in brain regions important for memory and cognition [242]. Genetic risk factors for VaD with associated neuronal and/or synaptic dysfunction are genes involved in the genesis of *CADASIL*, but also *ERBB*3. *ERBB*3 plays a role in neuroprotection and was found to be downregulated in the hippocampus of a vascular dementia rat model with modified two-vessel occlusion (2-VO) [243]. In this model, the *ERBB*3 downregulation was associated with vascular cognitive impairment and loss of CA1 pyramidal cells [244].

Furthermore, it was suggested that cell cycle-related phenomena may play a key role in the formation of AD pathology and neuronal cell death in AD, as well as in cerebrovascular diseases [245]. Smith et al. [245] observed elevated levels of Cyclin B1 expression in the CA1 region of volunteers with cerebrovascular disease, while cyclin E expression was elevated in the CA4 region in individuals with mixed dementia (AD and cerebrovascular disease). The authors assumed that cell cycle arrest may lead to pathological changes related either to AD or VaD.

4.2.3. Amyloid-ß and Tau Pathology

Amyloid plaques and the formation of neurofibrillary tangles are known as the "hallmark" lesions of AD [43,46,75,207]. Dysfunctional processing of the amyloid precursor protein and imbalances in the production and clearance pathways cause amyloid plaques, which are extracellular deposits formed by the accumulation of Aß peptides (Aß40 and Aß42) [75]. In contrast, neurofibrillary tangles are part of the tau pathology, where insoluble misfolded deposits of hyperphosphorylated tau are aggregated in neurons.

As characteristic neuropathological features for AD the neuritic plaque density and Braak stage for neurofibrillary tangles were greater in AD (2.57 and 4.71 respectively) compared to VaD (1.87 and 3.67 respectively) [79]. According to Mukaetova-Ladinska et al. [63] tangle density was 9-fold higher in AD subjects than in participants diagnosed VaD. However, also in neurovascular diseases, Aß is present (Table 3). According to Kalaria and Ballard [246] about one-third of subjects with VaD would have AD-type pathology at autopsy. Furthermore, 30 % of individuals with post-stroke dementia or subcortical VaD displayed concurrent Aß pathology in in-vivo Aß PET studies [247,248]. Aß-42 accumulation was also evident in subjects with multi-infarct dementia and was suggested to be similar to the Aß-42 accumulation observed in older participants (<70 years) with AD [161]. In fact, Lewis et al. [249] demonstrated that especially Aß-42 accumulation was present in AD as well as in VaD, although the mean amount of total Aß-42 in VaD was approximately 50 % of that in AD. Aging might contribute to the severity of Aß-42 accumulation in patients with VaD, as individuals older than 80 years had comparable Aß-42 concentration with those in AD in the temporal cortex [249]. Furthermore, Bibl et al. [64] evaluated the patterns of Aß peptides, total tau and phosphor-tau in the CSF and found a similar pattern of these neurochemical components in AD and mixed dementia. Tau-levels were increased in participants with probable AD diagnosis, definite AD with cerebrovascular disease and probable VaD diagnosis. Aß1-42 levels measured by ELISA were diminished in all dementia groups.

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The spreading pattern of Aß in AD-related cognitive impairment differs from individuals with subcortical vascular cognitive impairment (SVCI) [248]. In subjects with AD-related cognitive impairment, Aß accumulated first in the parietal and fronto-temporal regions before the occipital region. However, in VaD Aß is first excessively deposited in the parietal and occipital region, which may be connected with the predominant appearance of CAA in the occipital lobe [248] or an increased vulnerability for dysfunctional microvasculature in the posterior circulation [250]. Moreover, protein analysis by indirect ELISA revealed a distinct pattern of t-tau (total-tau) and p-tau (phosphorylated tau) distribution in both forms of dementia: Compared to VaD and controls, t-tau protein levels were higher in the frontal lobe and p-tau (for antibodies Ser202/Thr105 and Ser262) was increased in the temporal and frontal lobes of individuals with AD. Moreover, p-tau was increased, while Aß1-42 levels were decreased in the CSF of subjects with probable AD. In contrast p-tau and Aß1-42 levels in the CSF were not altered in subjects with VaD [64]. Therefore, the authors conclude that p-tau and Aß1-42 levels in the CSF sufficiently discriminate between probable AD and VaD. For VaD, the study of Mukaetova-Ladinska et al. [63] did also reveal a selective loss of t-tau protein compared with controls and AD subjects, which are supposed to be rather related to dysfunctional microvasculature architecture than neurofibrillary or amyloid pathology. There is also a link between the age of AD symptom onset and the extent of tau pathology in certain heavily affected regions and accelerated tau spreading has been associated with faster cognitive decline (Figure 2). Brain hubs were identified where tau aggregation was mainly present and these regions were essential parts of controlling and maintaining the cognitive performance in AD. A stronger tau signal in those brain regions in the PET predicted faster tau accumulation and suggested tau spreading through highly connected brain regions [251].

There is mounting evidence of Aß having powerful cerebrovascular effects (vascular Aß is a potent vasoconstrictor) [9,252]. Aß may induce ischemia and hypoperfusion. But also cerebrovascular insufficiency, resulting in hypoperfusion and hypoxia, may promote tau and tau phosphorylation as well as Aß production [9,252]. Indications for a potential link between hypoxic events and Aß production were provided by Zhang et al., [253] in which hypoxia-inducible factor-1 (HIF-1), a marker of hypoxia, supposedly mediated Aß production and the hypoxic effect of ß-secretase (BACE1). Eventually, this leads to a vicious circle in which cerebrovascular insufficiency and Aß progressively affect each other negatively. In this sense, it was also suggested that cerebral SVD impairs the clearance of Aß, explaining the possible mechanistic link between AD and cerebral SVD. In addition, tau formation was associated with increased cerebrovascular pathology in animal studies [248].

4.2.4. Brain Metabolism

Glucose is the main substrate for brain energy metabolism to support all cellular functions and can be measured by positron emission tomography (PET) [254–256]. Thus, regional cerebral metabolic rates for glucose reflect regional brain function.

For both forms of dementia, AD and VaD, glucose hypometabolism was reported (Table 4) [255]. Reduced glucose metabolism was found in the posterior parietal, precuneus, posterior cingulate, prefrontal and anterior hippocampal regions for both, AD and VaD [257]. Of these areas, glucose metabolism was in particular low for participants with AD in the precuneus, prefrontal area and the parahippocampal region [258]. Others also report a pronounced glucose hypometabolism in the association areas for AD subjects [255]. However, comparing the pattern of glucose metabolism among both forms of dementia, individuals with VaD showed a more widespread pattern of hypometabolism with the deep gray nuclei, cerebellum, primary cortices, middle temporal gyrus, and anterior cingulate gyrus mainly affected [255,257]. Similar results were obtained when comparing the preclinical stages of AD (amnestic MCI) and VaD (subcortical VCI): In subjects with preclinical AD hypometabolic regions were detected bilaterally in the parahippocampal and posterior cingulate gyri, the left superior temporal gyri, the left inferior parietal lobule, and right inferior frontal gyrus, while in individuals with preclinical VaD a decreased glucose metabolism

 doi:10.20944/preprints202309.1473.v2

mainly affected the thalamus, the insula, the superior temporal gyrus, the anterior cingulate gyrus, cingulum, right basal ganglia, cerebellum, and brainstem [259].

A strong link between an altered glucose metabolism and a genetic risk factor for AD is the *APOE* allele [260]. It was demonstrated that glucose hypometabolism in *APOE*4 carriers was evident before cognitive symptoms were present [260,261]. A list of AD genetic risk factors associated with glucose metabolism is provided by Cho et al. [260].

Table 4. compares features of brain metabolism in AD versus VaD. Abbreviations: **AD**: Alzheimer's disease; **VaD**: vascular dementia. **Table 4: metabolism in vascular dementia and Alzheimer's disease.**

Vascular dementia versus Alzheimer disease				
		similarities	differences	
			AD	VaD
hypometabolism (glucose)	prevalence	-	-	-
	location	• same volume of regions affected [255] • common pattern: posterior parietal, precuneus, posterior cingulate, prefrontal and anterior hippocampal regions [204,257]	• pronounced in association areas: hippocampal region, orbitofrontal, posterior cingulate and posterior parietal cortices [255,257] • in preclinical AD: bilateral parahippocampal, bilateral posterior cingulate, left superior temporal gyri, left inferior parietal lobule, and right inferior frontal gyrus [258]	• widespread in cerebral regions: deep gray nuclei, cerebellum, primary cortices, middle temporal gyrus and anterior cingulate cortex [255,257] • in preclinical VaD: thalamus, insula, superior temporal gyrus, anterior cingulate gyrus, cingulum, right basal ganglia, cerebellum, and brainstem [258]
	genetics		• *APOE* e.g. *APOE*4 [259,260] (detailed list in Cho et al. [259])	-

5. Conclusion

 doi:10.20944/preprints202309.1473.v2

New therapies to prevent or delay the onset of symptoms, slow progression or augment cognitive and behavioral symptoms for both AD and VaD. Although recent progress has been made in the development and approval of disease modifying therapies (DMTs) and symptomatic treatments for neuropsychiatric syndromes of AD [262], the same is not true for VaD. As elaborated in this review, both- the diagnosis and the development of novel therapeutic strategies- remains challenging for AD and VaD. We thus focused here to review similarities and differences between the two disease entities to identify factors which might improve diagnostic accuracy and conceptual strategies for new treatment approaches.

For improved diagnostic accuracy for the early detection of neurodegenerative signs but in particular the differentiation between AD and VaD we propose the following features:

1.) MR Imaging can reveal medial temporal lobe atrophy or entorhinal cortex atrophy as early neuromorphological markers for AD [206–208]. While medial temporal lobe atrophy can also be detected in VaD, brain atrophy in VaD is more globally distributed [26,55]. Other imaging biomarkers are microbleeds, lacunar infarcts, microinfarcts and white matter rarefaction. Their location can provide additional diagnostic clues: E.g. Microbleeds are located preferentially lobar, mainly in the occipital lobe in AD [168]. In contrast, a scattered distribution throughout the brain (with described involvement of frontal lobe and cerebellum) would be typical for VaD [163,263].

2.) CBF reduction and BBB breakdown are early pathological alterations in both diseases. Posterior-dominant reduction of CBF in AD and anterior-dominant reduction of CBF in VaD [152], as well as molecular factors related to the BBB, such as P-glycoprotein and plasma cyclophilin A levels can serve as early makers when distinguishing VaD and AD.

3.) Cerebrospinal fluid biomarkers such as Aß1-42 and p-tau levels proved to be valuable tools in discriminating AD and VaD [63,264]. Moreover, the reported selective loss of t-tau protein in VaD compared to Alzheimer's [63], might also help to distinguish both dementia forms.

4.) Glucose metabolism measured by positron emission topography (PET) show a different pattern of hypometabolism in both forms of dementia.

5.) Alzheimer's presents with a typical disease progression with the hippocampal region being affected first, whereas in VaD the course of the disease depends on the subtype with an abrupt, stepwise or gradual development of cognitive decline (Figure 2).

Therapeutic treatment have been challenging for VaD, due to the heterogeneity of the underlying pathology [9], but also for AD drug development, especially targeting Aß accumulation and tau pathology has been demanding [265–267]. The here reviewed neuropathological features highlight the considerable overlap of pathological alterations (Table 5) and shared basic pathomechanisms found in AD and VaD (Figure 3). Endothelial damage, BBB breakdown and hypoperfusion induce oxidative stress, inflammation and demyelination and thus trophic uncoupling in the neurovascular unit [9], aggravating damage to the endothelium and BBB. Leakage of the BBB and embolic events result in microbleeds and lacunar infarcts, microinfarcts and white matter rarefaction. Furthermore, a dysfunctional endothelium and BBB lead to the accumulation of neurotoxic molecules and Aß through impaired clearance, which in turn leads to neurodegeneration [73,89,126]. Deposition of Aß in the media and adventitia of small and mid-sized cerebral and leptomeningeal vessels aggravates cerebrovascular dysfunction, reinforcing a vicious cycle for the development of hemorrhagic and ischemic lesions with consecutive undersupply of essential metabolites to neurons resulting in neuronal dysfunction and ultimately neuronal death.

With regard to the vascular contribution in Alzheimer's, it is thus essential to target the cerebrovascular pathology in the treatment of Alzheimer's instead of solely focusing on the pure reduction of Aß or tau pathology. The interaction of Alzheimer's pathology with cerebrovascular pathology is still obscure. Further studies are necessary to evaluate the origin and impact of the

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cerebrovascular pathology and the destroyed homeostasis between neurons, glia and endothelial cells in AD and VaD to provide insight into novel therapeutic strategies. Improving the endothelial integrity and CBF might be a reasonable focus in novel treatment studies for AD, as well as VaD, as BBB dysfunction and reduced CBF are early pathomechanisms in both forms of dementia.

Table 5. compares the degree of different vascular and neuronal pathological features between AD and VaD. Abbreviations: **BBB**: blood-brain barrier; **CBF**: cerebral blood flow; **CAA**: cerebral amyloid angiopathy. "+" represents the presence of a pathological feature in minor peculiarity, "++" stands for a major pathological feature present and "+++" represents "hallmark" features for either AD or VaD.

Table 5: Overview of the compared pathological features.

Pathological features	AD	VaD
Atherosclerosis	+	+
BBB	+	+
CBF	+	+
CAA	++	+
Microbleeds	+	+++
Lacunar infarcts	+	+++
Microinfarcts	+	++
White matter rarefaction	+	+++
Atrophy	+++	+
Neuronal & synaptic loss	+++	++
Aß pathology	+++	+
Neurofibrillary pathology	+++	(-)
Hypometabolism	+	+

BBB: blood-brain barrier; **CBF**: cerebral blood flow; **CAA**: cerebral amyloid angiopathy.

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