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Review Article

Mixed dementia: Neglected clinical entity or nosographic artifice?

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ABSTRACT

Clinical and pathological data show that Alzheimer's disease (AD) and vascular dementia (VaD) are the most prevalent types of dementia in the elderly. Medically speaking, mixed dementia (MxD) is a heterogenous disorder mostly referred to the coexistence of AD and VaD. The weight of vascular contribution to AD phenotype is nowadays matter of debate. Despite great efforts in the field of neurodegeneration and cerebrovascular disease, controversy over the exact nature of their relation still remains, hampering progress in the specialty and raising doubts about the MxD concept validity. Is MxD a neglected clinical entity or a nosographic artifice? Starting from the assumption that recent advances in dementia classification and diagnostic criteria make this a propitious time to set up preventive and therapeutic strategies, this narrative review and opinion paper summarizes the literature concerning the questioned etiopathogenic overlap between AD and VaD and challenges the traditional view of MxD as the mere co-occurrence of different pure forms of dementia.

1. Background

The term mixed dementia (MxD) literally refers to the combination of more than one possible cause of dementia, of whatever type. In medical practice, it is mostly applied to those cases wherein there is clinical and/or pathological evidence of both dementia of Alzheimer type and cerebrovascular disease.

While in vivo criteria likely underestimate MxD frequency, data from neuroimaging and autopsy-based studies suggest that mixed pathology accounts for the majority of dementia cases among very old individuals [1]. Signs of cerebral microangiopathy and large infarcts are of frequent occurrence in patients otherwise diagnosed as suffering from Alzheimer's disease (AD), as well as hippocampal atrophy and hyperphosphorylated tau-protein aggregates, both typically deemed as markers of neurodegeneration, can be found among patients affected by vascular dementia (VaD) [2,3].

The role of vascular pathology as critical contributor to AD is a topic of current interest. Experimental and clinical evidence seems to challenge the traditional view that AD and VaD are distinct conditions and supports the notion of converging pathogenic mechanisms, thus making dementing disorders liable to preventive approaches [4]. On the other hand, the concept of MxD solely understood as the coexistence of different pure forms of dementia is still far from being abandoned.

After a brief excursus on the evolution of MxD concept over time, this paper updates current opinion on AD and VaD and their inner relation, paying attention to shared risk factors and pathophysiology. I report on recent literature concerning the overlap between neurodegeneration and vascular brain injury. In this field, one of the frequently-asked-questions from conference committees and audiences worldwide is: "Is MxD a neglected clinical entity or a nosographic artifice?". I try to answer this issue, winking to new and more fluid ways of thinking about dementia in the light of the emergent role of brain vasculature in the pathogenesis of neurodegenerative diseases, particularly AD.

2. Methodological considerations

This is a narrative review and opinion paper for which the author carried out an independent literature search in the PubMed electronic database from inception until September 2019. The literature search did not claim to be fully exhaustive and used the following key-terms in variable combinations: "mixed dementia", "Alzheimer's disease", "neurodegenerat*", "vascular dementia", and "cerebrovascular disease". The reference list of selected articles was screened to search for additional literature. Peer-reviewed publications from personal archives were also considered. The articles included in this paper were selected on the basis of their contribution to the global knowledge on the topic or explicit findings that made the publication relevant to the issue.

3. Historical context and origins of the terminology

The most common types of dementia in the elderly are AD and VaD

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[5]. Traditionally, the so-called hardening of the arteries was considered the leading cause of dementia since it was admitted that atherosclerosis lead to brain atrophy due to impaired blood supply. Interest in cognitive decline of vascular origin weakened in the 1980s, when the β-amyloid peptide was identified as the main component of parenchymal and vascular amyloid deposits. With the discovery of the amyloid precursor protein gene mutations in AD familial forms, the attention of the scientific community rapidly shifted on degenerative dementias [6]. Nevertheless, findings as microvascular injuries, endothelial proliferation, and neovascularization had already been described in the original Auguste Deter case besides senile plaques and neurofibrillary tangles, raising the suspicion to be on a wrong track when neglecting the vascular facet of the problem [7].

The term 'senile mixed dementia' was first introduced to depict the case of a demented patient with both degenerative and vascular features [8]. Some researchers felt the need to apply the definition of 'dementia of mixed arteriosclerotic and senile origin' to all cases in which degenerative and vascular lesions had such an extension that each could cause dementia by itself [9]. The concept of 'combined dementia' was then referred to AD pathology cases associated with ischemic lesions of various type and severity [10]. Based on the Alzheimer's Disease Diagnostic Treatment Center (ADDTC) criteria, it was argued that the diagnosis of MxD could be placed in the presence of an ischemic brain disease associated with a second systemic or brain disorder in causal relation with dementia [11]. A preferential use of the term 'AD with cerebrovascular disease', rather than MxD, was then recommended in the National Institute of Neurological Disorders and Stroke - Association Internationale pour le Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) international workshop to better emphasize that cerebrovascular diseases provide a minor contribution to dementia with respect to primary neurodegeneration [12]. According to the American Heart Association/American Stroke Association (AHA/ASA) statement, the construct of 'vascular cognitive impairment' was finally referred to the whole spectrum of cognitive impairment associated with cerebrovascular damage, including coexistent AD [13]. Through the years, it became clear that cerebral blood vessel pathology is only one contributor of vascular cognitive impairment, and all forms of deficits ranging from mild cognitive impairment to dementia fell into this clinical category.

4. Controversies on MxD clinicopathological significance

There are no doubts on the existence of MxD on a strictly clinical ground. However, a large evidence of both inter-individual stable differences as well as intra-individual variability in time characterizes the clinical picture. A cohort study reported much higher frequencies of depressed mood and focal motor or sensory findings among patients with MxD compared to those with AD [14]. In another study, MxD features were analyzed in comparison to AD and VaD, showing that focal signs were present in 20%, 4%, and 38% of the cases, respectively [15]. In some disease stages and in some patients, AD-like symptoms such as abnormal episodic or semantic memory and abstract thinking may predominate. In others, these may be less relevant than impaired executive functioning and processing speed, that more frequently impact the course of VaD. Few studies have attempted to establish prototypical MxD cognitive profile, disclosing a tendency to reduced performances in attention, visuo-construction tasks, and spatial abilities among patients with MxD of mild to moderate severity compared to those with AD [16–18].

Mixed symptoms coexist in a considerable proportion of patients, making difficult to distinguish cognitive decline due to AD from that sustained by cerebrovascular disease in view of the great overlap. In general, a conspicuous ability in integrating clinical data is required to make diagnosis of MxD.

Several criteria are available for clinical diagnosis of MxD, none of whom officially validated by means of neuropathological studies. In 1975, with the aim to quickly discriminate between pure degenerative and vascular types of dementia, Hachinski et al. proposed a bedside scale whose incorrect interpretation led researchers to consider MxD as the proper diagnosis for patients with intermediate scores, but this was not the original intention of the authors [19]. A lack of specificity in differentiating MxD from AD or VaD was later demonstrated by a meta-analysis which tested the utility of such scale in pathologically verified dementias [20]. According to the 10th revision of the International Classification of Diseases (ICD-10), MxD diagnosis can be attributed to patients who meet criteria for both AD and VaD [21]. In the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), MxD is catalogued under the umbrella term of 'major neurocognitive disorder due to multiple etiologies', a diagnosis that can be applied when there is evidence from history, physical examination, or laboratory findings that the disorder is the consequence of more than one etiological process [22]. The last position paper of the International Working Group (IWG) supported a refinement of MxD diagnostic work-up based on clinical and biomarker evidence of AD plus cerebrovascular disease: low concentrations of cerebrospinal fluid β-amyloid peptide and high tau-protein or increased amyloid PET tracer retention, together with neuroimaging signs of large or small vessel disease, are valid examples in this sense [23].

The reported high frequency of mixed brain pathology on autoptic examination suggests the biological plausibility of MxD without implying a clear diagnostic framework. As a matter of fact, there is still lack of consensus on the neuropathological definition of MxD, with no generally accepted criteria and inconstant operational tools across studies. Moreover, many elderly patients exhibit morphologic changes suggestive for AD, VaD, or MxD, but do not satisfy clinical requirements for dementia [24]. Proposed MxD neuropathological definitions include: the presence of moderate to severe concentrations of neuritic plaques in the neocortex and ≥ 2 gross cortical infarcts or ≥ 2 gross subcortical infarcts [25]; the combination of senile plaques and neurofibrillary tangles $> 5/mm^2$ in the hippocampal formation/neocortex and multifocal cerebral infarcts [26]; the presence of autopsy-proven AD according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) protocol and > 100 mL of cerebral infarct volume [27]; the combination of autopsy-proven AD (using accepted criteria) and multiple lacunes in the cortex, basal ganglia, thalamus, hippocampus, and white matter, or at least 30–50 mL of cerebral infarct volume [28].

5. Vascular contribution to AD: shared risk factors and mixed pathological burden

It is widely recognized that classical vascular factors provide an important contribution to AD [29,30]. The Rotterdam study, one of the first large studies which catalyzed attention on this issue, showed that many markers of atherosclerosis are associated with an increased risk of dementia, including AD [31]. Hypertension, diabetes, dyslipidemia, tobacco smoking, obesity, and a host of vascular vulnerabilities have been further outlined as reliable AD predictors [32–36].

The pivotal role of cerebrovascular dysfunction in AD is overall suggested by the finding that stroke may accelerate deterioration in patients diagnosed with AD or alternatively prompt a single step from the 'brain-at-risk' stage to that of dementia [37–39]. The latter is confirmed by the observation that one third of stroke patients develops a condition defined as post-stroke dementia, i.e. any dementia occurring after stroke irrespective if the leading cause is vascular, degenerative, or mixed [40].

The weight exerted by a high vascular burden in determining the presence and severity of AD was first quantified in the Nun study, a pioneering study conducted in the USA in which, among participants who met neuropathological criteria for AD, the presence of cerebral infarcts was associated with poorer cognitive functions and higher prevalence of dementia [41].

Apart from the occurrence of stroke, other mechanisms by which several markers of vascular disease may unmask subthreshold AD symptoms or facilitate AD progression are currently beginning to be elucidated. While most of these factors have been associated with large vessel disease, the advent of MRI as routine procedure has revealed a not negligible impact of cerebral microangiopathy on degenerative features.

In the last decades, it has been clarified that for similar clinical severity of dementia there is a lesser degree of AD pathology in patients with vascular lesions than in those without, thus advocating the cumulative effect of the processes involved in AD and VaD and providing support for the MxD concept validity [42]. The discovery of the relation between a certain vascular risk profile and AD does not deny the supposed degenerative mechanisms thought to underlie pure AD but allows researchers to hypothesize that vascular and degenerative pathways actually develop in parallel or have a mutual interaction possibly producing a synergistic effect [43].

6. The inner relation between AD and VaD. Is there a mechanistic link?

Many mechanisms of tissue injury may be crucial in the cascade through which cerebrovascular disease promotes damage and cognitive decline in patients with AD pathology. In this regard, several lines of evidence denote that cerebrovascular dysfunction contributes to neuronal loss and mental deterioration in AD and cannot be merely attributed to comorbid VaD [44].

Neurodegeneration is commonly defined as the progressive loss of structure and/or function of neurons that culminates in cellular atrophy and death. Regardless of dementia subtype, secondary degenerative changes frequently occur in patients with variably expressed vascular brain injury (micro or macroinfarcts, white matter lesions, hemorrhages, etc.) and result in white matter loss and cortical thinning [45,46]. Putative mechanisms involved in these changes mainly encompass pyramidal neuron retrograde degeneration, inflammatory reactions, and trans-synaptic effects [45,47–49].

Indeed, many molecular processes take place in the central nervous system at a microvascular level and may explain the so-called secondary neurodegeneration in a more extensive way. The neurovascular unit, a widely heterogeneous structure made of endothelial cells, pericytes, smooth muscle cells, neurons, and neuroglia, controls blood-brain barrier permeability and blood flow and maintains a stable chemical composition in the cerebral microenvironment, which is required for proper working of neurotransmission [44]. Vascular-derived pathophysiology in AD includes blood-brain barrier leakage, hypoperfusion/hypoxia, and endothelial metabolic dysfunction. Consistently observed in the course of several ischemic injuries and degenerative disorders, increasing levels of matrix metalloproteinase activity have been put in relation with the blood-brain barrier leakage and subsequent cascade of events that culminates in deposition of hemoglobin-related products, including iron, and generation of neurotoxic reactive oxygen species [50]. Oxidative stress in turn induces β-amyloid production and prompts tau-protein synthesis. Several studies have shown that mild hypoperfusion, termed oligoemia, not only affects protein synthesis, which is necessary for the synaptic plasticity mediating memory and learning, but also modulates amyloid precursor protein processing via selective augmentation of enzymes involved in the development of AD such as β-secretase and γ-secretase [51–53]. Moreover, imbalance in cerebrovascular metabolic functions leads to the release of a set of neurotoxic and inflammatory factors (nitric oxide, cytokines, chemokines, prostaglandins, etc.) that can trigger neuronal damage directly or indirectly by activating astrocytes and microglia [54]. These findings point to a potential interplay between vascular disease and neurodegeneration and suggest that cerebrovascular pathology and AD interact or alternatively are in cause-and-effect relation, despite that conclusive evidence for a causal link between the two is still lacking [55].

Conversely, some experimental studies highlight the possible vascular consequences of primary neurodegeneration [56]. One of the ways in which AD pathology may promote vascular pathology consists of resting cerebral blood flow reduction and vasoconstriction mediated by β-amyloid, resulting in increased susceptibility to ischemia [57,58]. Accumulation and deposit of β-amyloid fragments can also induce neuronal dysfunction, impair endothelial ability to relax vessels in vitro, and affect neurovascular coupling and autoregulation in mice overexpressing mutated amyloid precursor protein [57,59,60]. Thus, a vicious cycle can be identified whereby vascular insufficiency causes β-amyloid production, which in turn leads to the loss of vascular homeostasis.

7. Towards new ways of conceptualizing MxD

In the course of the years, some theories have emerged in favor of a vascular origin of sporadic AD cases [61,62]. In the author opinion, the demonstration of a vascular impairment in AD goes beyond the search for the primary trigger of neurodegeneration, thus reversing the paradigm of a not solvable conflict between the amyloid and vascular hypotheses and shedding light on alternative classifications of dementia (Fig. 1). As anticipated, the concept of vascular cognitive impairment encompasses a broad range of entities such as mixed vascular and AD-type pathologies [13,63,64]. Noteworthy, the importance of vascular cognitive impairment approach relies on its drive to overcome the categorial contraposition between AD and VaD on a clinical ground, starting from the awareness that cerebrovascular lesions are the main preventable and treatable components of cognitive decline.

Another issue of consideration is the possible link between AD and white matter hyperintensities of vascular or non-vascular origin [65]. Among small vessel diseases, cerebral amyloid angiopathy is now worthy of mention since, besides being recognized as a cause of hemorrhagic stroke and transient focal neurological episodes, it has been linked with brain atrophy and progressive cognitive decline through three different pathways: the local effect of tissue destruction by intracerebral hemorrhage, the effect of eventually concomitant AD pathology, or pathomechanisms other than parenchymal hematoma and AD [66]. While the question of whether cerebral amyloid angiopathy is an independent cause of neurodegeneration is still unanswered, little doubts remain on its potential to alter cerebrovascular reactivity. In this sense, the need to incorporate markers of vascular dysfunction into a new AD definition appears to be cogent [67].

According to the above reported body of literature and given the observation that in medical practice the coexistence of mixed features is all but an exception among demented patients, one can assume that MxD is a real clinical entity. What is notable is that albeit epidemiological data depict MxD as the most prevalent type of dementia, a variable degree of uncertainty regarding the diagnostic management and the lack of dedicated pharmacological studies make it not considered as such by some medical and public health communities or by society at large. If anything, there is debate about the question of whether MxD is a mere nosographic artifice (the sum of AD and VaD, i.e. a reflection of scientific classification trends) rather than a spectrum of disease with ascertained neurobiological bases. The latter suggestion may drive therapeutic possibilities related to both AD vascular hallmarks and VaD degenerative stigmata. Consistently with observational data indicating that large-scale treatment of vascular risk factors could slow the rate of cognitive decline, some approaches have been attempted to restore β-amyloid clearance and stabilize endothelial damage in ischemic brain regions [68,69]. In parallel, interventions oriented to neuroprotection show promising results when declined into disease-modifying therapy with pleiotropic compounds specifically targeting neuronal death, compensatory plasticity, and protein misfolding with autophagy [70–72].

Although most evidence that AD and VaD are interconnected comes from animal model studies, a large amount of clinical observations

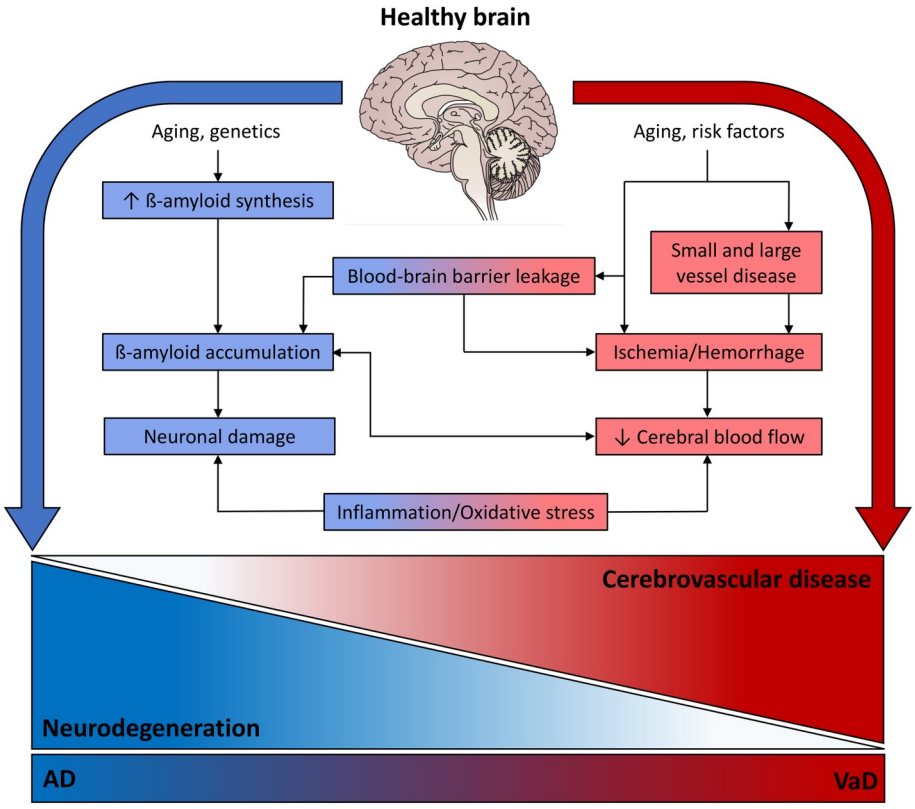

Fig. 1. Conceptual model of dementia spectrum. In the upper panel: aging, genetics, and various environmental factors are key-determinants of cognitive decline according to a trans-nosographic dimension encompassing neurodegeneration and cerebrovascular disease. Damage to the neurovascular unit plays a central role potentially leading to both amyloid plaque deposits and cerebral hypoperfusion. In the lower panel: a gradient of mixed features is interposed between neurodegenerative and cerebrovascular burden. AD and VaD pure expressions are represented at the left and right side, respectively. AD indicates Alzheimer's disease, VaD vascular dementia.

Table 1
Data-driven and putative pathways of inter-relation between AD and VaD supporting the biological plausibility of MxD. AD indicates Alzheimer's disease, VaD vascular dementia.

Vascular burden → AD	Degenerative burden → VaD
A. Tissue damage	**A. Tissue damage**
1. Macroscopic infarcts	1. Extracellular plaques (β-amyloid accumulation)
2. Microinfarcts	2. Intracellular tangles (hyperphosphorylated tau-protein aggregates)
3. Hemorrhages	3. Brain atrophy
4. White matter hyperintensities	
B. Impaired neurovascular coupling	**B. Loss of vascular autoregulation**
1. Hypoperfusion/hypoxia (↑ secretases)	1. Blood-brain barrier leakage
2. Blood-brain barrier leakage (↑ matrix metalloproteinases)	2. Pro-inflammatory imbalance (↑ oxidative stress)
3. Endothelial dysfunction (↑ inflammatory toxins)	3. Endothelial dysfunction (↓ vasodilation in vitro)
C. Secondary neurodegeneration (neuronal and oligodendrocyte loss, astrocytosis, microgliosis)	**C. "Secondary" cerebrovascular injury (large and small vessel disease)**
1. Retrograde degeneration	1. Impaired resting blood flow (oligoemia)
2. Inflammatory reactions	2. Impaired amyloid clearance
3. Trans-synaptic effect	3. Amyloid angiopathy-related vasculopathic changes

support this prospect and confirm the need to bridge the translational gap. The emerging role of cerebral blood vessels in the pathogenesis of many degenerative diseases suggests that advances in molecular biology are advisable to increase the number of neurovascular markers which are specific for different cell types. Moreover, the improvement of diagnostic instruments and conceptualization of new neuroimaging modalities could have the potential to better investigate the regional pathophysiology in the living human brain, with particular reference to the endothelium inflammatory phenotype [73].

8. Conclusive remarks

This narrative review and opinion paper provides an overview of MxD concept definition, diagnosis, and pathophysiology, stressing the idea that vascular and degenerative changes are inextricably linked substrates of age-related cognitive impairment (Table 1). As opposite to the leading opinion which invokes the recourse to more detailed disease specifiers (e.g., AD with cerebrovascular disease), the use of the ancient term MxD moves from the attempt to underline the unclear ontological status of this disorder at crossroads between clinical perspectives and nosographic needs.

The wide-ranging repertoire of MxD clinicopathological picture often complicates the diagnostic assessment. Nevertheless, it stands to reason that mixed pathology co-occurs in the majority of dementia cases and possibly derives from common pathways. Conflicting results come from studies exploring one of the most prominent research trajectories in the field, i.e. the relation between in vivo biomarkers of β-amyloid burden and small vessel diseases [74,75]: the recent

observation that elevated florbetapir-PET signal correlates with increased white matter hyperintensities is inter alia in agreement with the putative role of cerebral microangiopathies in disruption of interstitial fluid bulk flow and paravascular mechanisms of β-amyloid clearance [76].

Far from being solved, the fascinating dilemma of MxD ultimately offers the opportunity to expand the framework of dementia research and shift proteogenomics applications from neurodegeneration to vascular and metabolic dysfunction and other unforeseen processes impacting cognition. The topic encloses powerful implications aimed at elucidating AD pathophysiology and opening new avenues for prevention and treatment of full-spectrum dementia.

Declaration of Competing Interest

The author has no conflicts of interest to disclose.

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References

[1] A.D. Korczyn, Mixed dementia - the most common cause of dementia, Ann. N. Y. Acad. Sci. 977 (2002) 129–134.
[2] L.M. Allan, E.N. Rowan, M.J. Firbank, A.J. Thomas, S.W. Pary, T.M. Polvikoski, J.T. O'Brien, R.N. Kalaria, Long term incidence of dementia, predictors of mortality and pathological diagnosis in older stroke survivors, Brain 134 (2012) 3716–3727.
[3] K.A. Jellinger, J. Attems, Prevalence and pathogenic role of cerebrovascular lesions in Alzheimer disease, J. Neurol. Sci. 229-230 (2005) 37–41.
[4] C. Iadecola, The overlap between neurodegenerative and vascular factors in the pathogenesis of dementia, Acta Neuropathol. 120 (2010) 287–296.
[5] W.M. van der Flier, P. Scheltens, Epidemiology and risk factors of dementia, J. Neurol. Neurosurg. Psychiatry 76 (S5) (2005) V2–V7.
[6] J.V. Bowler, Modern concept of vascular cognitive impairment, Br. Med. Bull. 83 (2007) 291–305.
[7] A. Alzheimer, Über eine eigenartige erkrankung der hirnrinde, Allgemeine Zeitschrift fÜr Psychiatrie und Psychisch-Gerichtliche Medizin 64 (1907) 146–148.
[8] J. Delay, S. Brion, Démence sénile mixte, in: J. Delay, S. Brion (Eds.), Les Démences Tardives, Masson, Paris, France, 1962, pp. 195–201.
[9] B.E. Tomlinson, G. Blessed, M. Roth, Observations on the brains of demented old people, J. Neurol. Sci. 11 (1970) 205–242.
[10] P.K. Mölsa, L. Paljärvi, J.O. Rinne, U.K. Rinne, E. Säkö, Validity of clinical diagnosis in dementia: a prospective clinicopathological study, J. Neurol. Neurosurg. Psychiatry 48 (1985) 1085–1090.
[11] H. Chui, J.I. Victoroff, D. Margolin, W. Jagust, R. Shankle, R. Katzman, Criteria for the diagnosis of ischemic vascular dementia proposed by the state of California Alzheimer's disease diagnostic and treatment Centers, Neurology 42 (1992) 473–480.
[12] G.C. Roman, T.K. Tatemichi, T. Erkinjuntti, J.L. Cummings, J.C. Masdeu, J.H. Garcia, L. Amaducci, J.M. Orgogozo, A. Brun, A. Hofman, D.M. Moody, M.D. O'Brien, T. Yamaguchi, J. Grafmam, B.P. Drayer, D.A. Bennett, M. Fisher, J. Ogata, E. Kokmen, F. Bermejo, P.A. Wolf, P.B. Gorelick, K.L. Bick, A.K. Pajeau, M.A. Bell, C. DeCarli, A. Culebras, A.D. Korczyn, J. Bogousslavsky, A. Hartmann, P. Scheinberg, Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop, Neurology 43 (1993) 250–260.
[13] P.B. Gorelick, A. Scuteri, S.E. Black, C. Decarli, S.M. Greenberg, C. Iadecola, L.J. Launer, S. Laurent, O.L. Lopez, D. Nyenhuis, R.C. Petersen, J.A. Schneider, C. Tzourio, D.K. Arnett, D.A. Bennett, H.C. Chui, R.T. Higashida, R. Lindquist, P.M. Nilsson, G.C. Roman, F.W. Sellke, S. Seshadri, American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular Surgery and Anesthesia, Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American HeartAssociation/American Stroke Association, Stroke 42 (2011) 2672–2713.
[14] J. Corey-Bloom, D. Galasko, C.R. Hofstetter, J.E. Jackson, L.J. Thal, Clinical features distinguishing large cohorts with possible AD, probable AD, and mixed dementia, J. Am. Geriatr. Soc. 41 (1993) 31–37.
[15] K. Rockwood, C. Macknight, C. Wentzel, S. Black, R. Bouchard, S. Gauthier, H. Feldman, D. Hogan, A. Kertesz, P. Montgomery, The diagnosis of "mixed" dementia in the consortium for the investigation of vascular impairment of cognition (CIVIC), Ann. N. Y. Acad. Sci. 903 (2000) 522–528.
[16] Y. Dong, D.Z. Gan, S.Z. Tay, W.I. Koay, S.L. Collinson, S. Hilal, N. Venketasubramanian, C. Chen, Patterns of neuropsychological impairment in Alzheimer's disease and mixed dementia, J. Neurol. Sci. 333 (2013) 5–8.
[17] H.S. Kang, J.H. Kwon, S. Kim, D.L. Na, S.Y. Kim, J.H. Lee, S.H. Han, S.H. Choi, S. Kim, B.J. Carroll, D.K. Kim, Comparison of neuropsychological profiles in patients with Alzheimer's disease and mixed dementia, J. Neurol. Sci. 369 (2016) 134–138.
[18] B.R. Reed, D.M. Mungas, J.H. Kramer, W. Ellis, H.V. Vinters, C. Zarow, W.J. Jagust, H.C. Chui, Profiles of neuropsychological impairment in autopsy-defined Alzheimer's disease and cerebrovascular disease, Brain 130 (P3) (2007) 731–739.
[19] V.C. Hachinski, L.D. Iliff, E. Zilhka, G.H. Du Boulay, V.L. McAllister, J. Marshall, R.W. Russell, L. Symon, Cerebral blood flow in dementia, Arch. Neurol. 32 (1975) 632–637.
[20] J.T. Moroney, E. Bagiella, V.C. Hachinski, P.K. Mölsä, L. Gustafson, A. Brun, P. Fischer, T. Erkinjuntti, W. Rosen, M.C. Paik, T.K. Tatemichi, D.W. Desmond, Misclassification of dementia subtype using the Hachinski ischemic score: results of a meta-analysis of patients with pathologically verified dementias, Ann. N. Y. Acad. Sci. 826 (1997) 490–492.
[21] World Health Organization, The ICD-10 classification of mental and behavioral disorders: Diagnostic criteria for research, Geneva, Switzerland, 1993.
[22] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), (2013) Washington, DC.
[23] B. Dubois, H.H. Feldman, C. Jacova, H. Hampel, J.L. Molinuevo, K. Blennow, S.T. DeKosky, S. Gauthier, D. Selkoe, R. Bateman, S. Cappa, S. Crutch, S. Engelborghs, G.B. Frisoni, N.C. Fox, D. Galasko, M.O. Habert, G.A. Jicha, A. Nordberg, F. Pasquier, G. Rabinovici, P. Robert, C. Rowe, S. Salloway, M. Sarazin, S. Epelbaum, L.C. de Souza, B. Vellas, P.J. Visser, L. Schneider, Y. Stern, P. Scheltens, J.L. Cummings, Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria, Lancet Neurol. 13 (2014) 614–629.
[24] P. Giannakopoulos, P.R. Hof, J.P. Michel, J. Guimon, C. Bouras, Cerebral cortex pathology in aging and Alzheimer's disease: a quantitative survey of large hospital-based geriatric and psychiatric cohorts, Brain Res. Brain Res. Rev. 25 (1997) 217–245.
[25] M.F. Mendez, A.R. Mastri, J.H. Sung, W.H. Frey 2nd, Clinically diagnosed Alzheimer disease: neuropathologic findings in 650 cases, Alzheimer Dis. Assoc. Disord. 6 (1992) 35–43.
[26] P. Giannakopoulos, P.R. Hof, S. Mottier, J.P. Michel, C. Bouras, Neuropathological changes in the cerebral cortex of 1258 cases from a geriatric hospital: retrospective clinicopathological evaluation of a 10-year autopsy population, Acta Neuropathol. 87 (1994) 456–468.
[27] P.G. Ince, F.K. McArthur, E. Bjertness, A. Torvik, J.M. Candy, J.A. Edwardson, Neuropathological diagnoses in elderly patients in Oslo: Alzheimer's disease, Lewy body disease, vascular lesions, Dementia 6 (1995) 162–168.
[28] K.A. Jellinger, J. Attems, Neuropathological evaluation of mixed dementia, J. Neurol. Sci. 257 (2007) 80–87.
[29] H.C. Chui, C. Zarow, W.J. Mack, W.G. Ellis, L. Zheng, W.J. Jagust, D. Mungas, B.R. Reed, J.H. Kramer, C.C. Decarli, M.W. Weiner, H.V. Vinters, Cognitive impact of subcortical vascular and Alzheimer's disease pathology, Ann. Neurol. 60 (2006) 677–687.
[30] M. Kivipelto, E.L. Helkala, M.P. Laakso, T. Hänninen, M. Hallikainen, K. Alhainen, H. Soininen, J. Tuomilehto, A. Nissinen, Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study, BMJ 322 (2001) 1447–1451.
[31] A. Hofman, A. Ott, M.M. Breteler, M.L. Bots, A.J. Slooter, F. van Harskamp, C.N. van Duijn, C. Van Broeckhoven, D.E. Grobbee, Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study, Lancet 349 (1997) 151–154.
[32] G.J. Biessels, I.J. Deary, C.M. Ryan, Cognition and diabetes: a lifespan perspective, Lancet Neurol. 7 (2008) 184–190.
[33] M.M. Breteler, Vascular risk factors for Alzheimer's disease: an epidemiologic perspective, Neurobiol. Aging 21 (2000) 153–160.
[34] L.J. Launer, G.W. Ross, H. Petrovich, K. Masaki, D. Foley, L. White, R.J. Havlik, Midlife blood pressure and dementia: the Honolulu-Asia aging study, Neurobiol. Aging 21 (2000) 49–55.
[35] J.A. Luchsinger, C. Reitz, L.S. Honig, M.X. Tang, S. Shea, R. Mayeux, Aggregation of vascular risk factors and risk of incident Alzheimer disease, Neurology 65 (2005) 545–551.
[36] I. Skoog, B. Lernfelt, S. Landahl, B. Palmertz, L.A. Andreasson, L. Nilsson, G. Persson, A. Odén, A. Svanborg, 15-year longitudinal study of blood pressure and dementia, Lancet 347 (1996) 1141–1145.
[37] R.N. Kalaria, The role of cerebral ischemia in Alzheimer's disease, Neurobiol. Aging 21 (2000) 321–330.
[38] A. Nucera, V. Hachinski, Cerebrovascular and Alzheimer disease: fellow travelers or partners in crime? J. Neurochem. 144 (2018) 513–516.
[39] L. Pantoni, A. Poggesi, D. Inzitari, Cognitive decline and dementia related to cerebrovascular diseases: some evidence and concepts, Cerebrovasc. Dis. 27 (S1) (2009) 191–196.
[40] M. Pasi, A. Poggesi, E. Salvadori, L. Pantoni, Post-stroke dementia and cognitive impairment, Front. Neurol. Neurosci. 30 (2012) 65–69.
[41] D.A. Snowdon, L.H. Greiner, J.A. Mortimer, K.P. Riley, P.A. Greiner, W.R. Markesbery, Brain infarction and the clinical expression of Alzheimer disease, The Nun study, JAMA 277 (1997) 813–817.
[42] D. Zekry, J.J. Hauw, G. Gold, Mixed dementia: epidemiology, diagnosis, and treatment, J. Am. Geriatr. Soc. 50 (2002) 1431–1438.
[43] D. Zekry, C. Duyckaerts, R. Moulias, J. Belmin, C. Geoffre, F. Herrmann, J.J. Hauw, Degenerative and vascular lesions of the brain have synergistic effects in dementia of the elderly, Acta Neuropathol. 103 (2002) 481–487.
[44] B.V. Zlokovic, Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders, Nat. Rev. Neurosci. 12 (2011) 723–738.
[45] M. Dichgans, D. Leys, Vascular cognitive impairment, Circ. Res. 120 (2017) 573–591.
[46] M. Duering, R. Righart, F.A. Wollenweber, V. Zietemann, B. Gesierich, M. Dichgans,

Acute infarcts cause focal thinning in remote cortex via degeneration of connecting fiber tracts, Neurology 84 (2015) 1685–1692.
[47] V. Foster, A.E. Oakley, J.Y. Slade, R. Hall, T.M. Polvikoski, M. Burke, A.J. Thomas, A. Khundakar, L.M. Allan, R.N. Kalaria, Pyramidal neurons of the prefrontal cortex in post-stroke, vascular and other ageing-related dementias, Brain 137 (2014) 2509–2521.
[48] P. Jindahra, A. Petrie, G.T. Plant, The time course of retrograde trans-synaptic degeneration following occipital lobe damage in humans, Brain 135 (2012) 534–541.
[49] M. Schroeter, P. Zickler, D.T. Denhardt, H.P. Hartung, S. Jander, Increased thalamic neurodegeneration following ischemic cortical stroke in osteopontin-deficient mice, Brain 129 (2006) 1426–1437.
[50] G.A. Rosenberg, Matrix metalloproteinases and their multiple roles in neurodegenerative diseases, Lancet Neurol. 8 (2009) 205–216.
[51] M. Guglielmotto, M. Aragno, R. Autelli, L. Giliberto, E. Novo, S. Colombatto, O. Danni, M. Parola, M.A. Smith, G. Perry, E. Tamagno, M. Tabaton, The up-regulation of BACE1 mediated by hypoxia and ischemic injury: role of oxidative stress and HIF1α, J. Neurochem. 108 (2009) 1045–1056.
[52] C. Iadecola, Neurovascular regulation in the normal brain and in Alzheimer's disease, Nat. Rev. Neurosci. 5 (2004) 347–360.
[53] L. Li, X. Zhang, D. Yang, G. Luo, S. Chen, W. Le, Hypoxia increases Aβ generation by altering β- and γ-cleavage of APP, Neurobiol. Aging 30 (2009) 1091–1098.
[54] C.K. Glass, K. Saijo, B. Winner, M.C. Marchetto, F.H. Gage, Mechanisms underlying inflammation in neurodegeneration, Cell 140 (2010) 918–934.
[55] C. Iadecola, R.F. Gottesman, Cerebrovascular alterations in Alzheimer disease, Circ. Res. 123 (2018) 406–408.
[56] C. Iadecola, The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease, Neuron 96 (2017) 17–42.
[57] K. Niwa, K. Kazama, L. Younkin, S.G. Younkin, G.A. Carlson, C. Iadecola, Cerebrovascular autoregulation is profoundly impaired in mice overexpressing amyloid precursor protein, Am. J. Physiol. Heart Circ. Physiol. 283 (2002) H315–H323.
[58] F. Zhang, C. Eckman, S. Younkin, K.K. Hsiao, C. Iadecola, Increased susceptibility to ischemic brain damage in transgenic mice overexpressing the amyloid precursor protein, J. Neurosci. 17 (1997) 7655–7661.
[59] C. Iadecola, F. Zhang, K. Niwa, C. Eckman, S.K. Turner, E. Fischer, S. Younkin, D.R. Borchelt, K.K. Hsiao, G.A. Carlson, SOD1 rescues cerebral endothelial dysfunction in mice overexpressing amyloid precursor protein, Nat. Neurosci. 2 (1999) 157–161.
[60] T. Thomas, G. Thomas, C. McLendon, T. Sutton, M. Mullan, β-amyloid-mediated vasoactivity and vascular endothelial damage, Nature 380 (1996) 168–171.
[61] J.C. de la Torre, Alzheimer disease as a vascular disorder: nosological evidence, Stroke 33 (2002) 1152–1162.
[62] J.C. de la Torre, Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics, Lancet Neurol. 3 (2004) 184–190.
[63] J.T. O'Brien, T. Erkinjuntti, B. Reisberg, G. Roman, T. Sawada, L. Pantoni, J.V. Bowler, C. Ballard, C. DeCarli, P.B. Gorelick, K. Rockwood, A. Burns, S. Gauthier, S.T. DeKosky, Vascular cognitive impairment, Lancet Neurol. 2 (2003) 89–98.
[64] V. Hachinski, C. Iadecola, R.C. Petersen, M.M. Breteler, D.L. Nyenhuis, S.E. Black, W.J. Powers, C. DeCarli, J.G. Merino, R.N. Kalaria, H.V. Vinters, D.M. Holtzman, G.A. Rosenberg, A. Wallin, M. Dichgans, J.R. Marler, G.G. Leblanc, National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards, Stroke 37 (2006) 2220–2241.
[65] E.E. Smith, Cerebral amyloid angiopathy as a cause of neurodegeneration, J. Neurochem. 144 (2018) 651–658.
[66] J. Alber, S. Alladi, H.J. Bae, D.A. Barton, L.A. Beckett, J.M. Bell, S.E. Berman, G.J. Biessels, S.E. Black, I. Bos, G.L. Bowman, E. Brai, A.M. Brickman, B.L. Callahan, R.A. Corriveau, S. Fossati, R.F. Gottesman, D.R. Gustafson, V. Hachinski, K.M. Hayden, A.M. Helman, T.M. Hughes, J.D. Isaacs, A.L. Jefferson, S.C. Johnson, A. Kapasi, S. Kern, J.C. Kwon, J. Kukolja, A. Lee, S.N. Lockhart, A. Murray, K.E. Osborn, M.C. Power, B.R. Price, H.F.M. Rhodius-Meester, J.A. Rondeau, A.C. Rosen, D.L. Rosene, J.A. Schneider, H. Scholtzova, C.E. Shaaban, N.C.B.S. Silva, H.M. Snyder, W. Swardfager, A.M. Troen, S.J. van Veluw, P. Vemuri, A. Wallin, C. Wellington, D.M. Wilcock, S.X. Xie, A.H. Hainsworth, White matter hyperintensities in vascular contributions to cognitive impairment and dementia (VCID): knowledge gaps and opportunities, Alzheimers Dement. (N. Y.) 5 (2019) 107–117.
[67] M.D. Sweeney, A. Montagne, A.P. Sagare, D.A. Nation, L.S. Schneider, H.C. Chui, M.G. Harrington, J. Pa, M. Law, D.J.J. Wang, R.E. Jacobs, F.N. Doubal, J. Ramirez, S.E. Black, M. Nedergaard, H. Benveniste, M. Dichgans, C. Iadecola, S. Love, P.M. Bath, H.S. Markus, R.A. Salman, S.M. Allan, T.J. Quinn, R.N. Kalaria, D.J. Werring, R.O. Carare, R.M. Touyz, S.C.R. Williams, M.A. Moskowitz, Z.S. Katusic, S.E. Lutz, O. Lazarov, R.D. Minshall, J. Rehman, T.P. Davis, C.L. Wellington, H.M. González, C. Yuan, S.N. Lockhart, T.M. Hughes, C.L.H. Chen, P. Sachdev, J.T. O'Brien, I. Skoog, L. Pantoni, D.R. Gustafson, G.J. Biessels, A. Wallin, E.E. Smith, V. Mok, A. Wong, P. Passmore, F. Barkof, M. Muller, M.M.B. Breteler, G.C. Román, E. Hamel, S. Seshadri, R.F. Gottesman, M.A. van Buchem, Z. Arvanitakis, J.A. Schneider, L.R. Drewes, V. Hachinski, C.E. Finch, A.W. Toga, J.M. Wardlaw, B.V. Zlokovic, Vascular dysfunction - the disregarded partner of Alzheimer's disease, Alzheimers Dement. 15 (2019) 158–167.
[68] P.T. Nelson, Cerebrovascular pathology and Alzheimer's disease, Lancet Neurol. 15 (2016) 895–896.
[69] R. Valenti, L. Pantoni, H.S. Markus, Treatment of vascular risk factors in patients with a diagnosis of Alzheimer's disease: a systematic review, BMC Med. 12 (2014) 160.
[70] R. Bordet, R. Ihl, A.D. Korczyn, G. Lanza, J. Jansa, R. Hoerr, A. Guekht, Towards the concept of disease-modifier in post-stroke or vascular cognitive impairment: a consensus report, BMC Med. 15 (2017) 107.
[71] J.T. O'Brien, A. Thomas, Vascular dementia, Lancet 386 (2015) 1698–1706.
[72] I. Skoog, A.D. Korczyn, A. Guekht, Neuroprotection in vascular dementia: a future path, J. Neurol. Sci. 322 (2012) 232–236.
[73] M.D. Sweeney, K. Kisler, A. Montagne, A.W. Toga, B.V. Zlokovic, The role of brain vasculature in neurodegenerative disorders, Nat. Neurosci. 21 (2018) 1318–1331.
[74] T.J. Haight, S.M. Landau, O. Carmichael, C. Schwarz, C. DeCarli, W.J. Jagust, Alzheimer's Disease Neuroimaging Initiative, Dissociable effects of Alzheimer disease and white matter hyperintensities on brain metabolism, JAMA Neurol. 70 (2013) 1039–1045.
[75] L.C. Rutten-Jacobs, F.E. de Leeuw, L. Geurts-van Bon, M.C. Gordinou de Gouberville, A.N. Schepens-Franke, P.J. Dederen, W.G. Spliet, P. Wesseling, A.J. Kiliaan, White matter lesions are not related to β-amyloid deposition in an autopsy-based study, Curr. Gerontol. Geriatr. Res. 2011 (2011) 826862.
[76] M. Marnane, O.O. Al-Jawadi, S. Mortazavi, K.J. Pogorzelec, B.W. Wang, H.H. Feldman, G.Y. Hsiung, Alzheimer's disease neuroimaging initiative, periventricular hyperintensities are associated with elevated cerebral amyloid, Neurology 86 (2016) 535–543.