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Mixed Pathology and Alzheimer's Disease

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In elderly individuals with dementia, it is increasingly established that mixed brain pathologies are the cause. Pathological changes typical of Alzheimer's disease have been observed to coexist with vascular problems associated with vascular dementia. Coexistence with Lewy bodies is also frequently observed. In some cases, brain changes associated with all three conditions coexist – Alzheimer's disease, vascular dementia and dementia with Lewy bodies. Here, we review the co-morbidities of Alzheimer's disease, their relevance to disease progression, and the presence of certain risk factors that also appear to influence disease progression.

Key words: Alzheimer's disease, mixed pathology

Introduction

The National Institute on Aging-Alzheimer's Association Task Force on Alzheimer's Disease (AD) diagnoses AD based on brain pathology at autopsy or in vivo with the use of biomarkers rather than clinical presentation [13]. They view the disease as a sequence with a long preclinical phase along with cognitive impairment developing over many years, accompanied by an accumulation of AD markers that begins decades before the manifestation of clinical signs.

Although AD is the most common cause of dementia, it can be accompanied by a number of other pathologies. AD-pathology increases with age, but at the same time, many other brain diseases that affect cognitive functions develop as well. Examples are cerebrovascular changes such as heart attacks, atherosclerosis and arteriosclerosis, changes in the white matter of the brain, Lewy body disease and hippocampal sclerosis [18]. Although each of these dementia-causing pathologies develop differently, they are not mutually exclusive. Several studies show that a large percentage of elderly people, regardless of whether they have symptoms of dementia or not, are carriers of different pathologies in the brain – the so-called mixed pathology [27]. Autopsy brains of patients diagnosed with AD often show mixed pathology. In very few of

the cases in which AD is indicated as the main diagnosis, solely neuropathological findings characteristic of AD are found at autopsy [28]. In patients diagnosed with AD, where autopsy results show the presence of AD-pathology, vascular and other types of pathologies are very often found as well [25, 29].

Role of the cerebrovascular dysfunction

A number of studies demonstrate the role of cerebrovascular dysfunction as an important risk factor in the development of AD. Cerebrovascular dysfunction is found earlier than cognitive decline and before the formation of Aβ-deposits [9]. Cerebrovascular morphological changes, blood-brain barrier dysfunction and reduced cerebral blood flow are associated with the development of AD [12]. Another pathological hallmark of AD that also contributes to vascular dysfunction is the presence of Aβ deposits in the walls of cerebral blood vessels, referred to as cerebral amyloid angiopathy, which is also involved in the development of the pathology [23].

Electron microscopic studies show that degenerated small blood vessels, including capillaries, are closely associated with amyloid deposits in senile plaques. There are suggestions that it is amyloid angiopathy of small blood vessels and degeneration of capillaries that leads to a lack of energy of the surrounding nerve cells and their degeneration. The results of very early studies by several working groups give them reason to assume that blood vessels play a major role in the formation of senile plaques. In examining the brains of a large number of patients who died with a diagnosis of AD, Joachim et al. (1988) [16] observed that "at least a minimal degree of amyloid angiopathy is found in any brain that has the histopathological changes characteristic of AD". According to Miyakawa (2010) [22], these results strongly support the hypothesis that one of the main reasons for the development of AD pathology are changes in the blood-brain barrier.

Age-related and individual risks

Any pathology that accompanies AD is an additional burden on the brain, which increases the risk of developing dementia [2, 11]. The probability of developing different pathologies increases with age, and therefore, in the oldest people, mixed pathology is the most common cause of developing dementia [14]. Matthews et al. (2009) [21] show that co-morbidities may be the cause of half and more dementias compared to AD-pathology. With advancing age, AD- and non-AD-type pathologies accumulate, so the proportion of mixed pathology grows, as does the risk of developing dementia. Combinations of different pathologies may be most diverse and the contribution of each to the development of dementia may be different in different individuals [7].

Understanding the role of different pathologies is important for assessing the risk factors leading to the development of AD. In their study, Boyle et al. (2013) [6] show that known types of neurodegenerative pathologies can explain less than half of the observed cognitive impairment in old age. This may be due to as yet unexplained pathological processes, but it may also be due to individual differences in the ability of the brain to protect itself from the development of pathologies [3].

It is known that the morphological signs of AD, as well as other known pathologies, are not clearly interrelated with the impairment of cognitive functions. In clinicopathological studies and with the use of biomarkers, it has been shown that at the same degree of manifestation of pathological changes, some individuals have clinical symptoms, while others have no deterioration [4]. This likely means that some individuals can develop resilience and respond flexibly to pathological processes,

allowing them to compensate for a greater degree of pathological changes than others. This has been termed cognitive or neuronal reserve capacity [3]. The biological basis of neuronal reserve includes cellular, synaptic, and biochemical pathways [1]. These may involve synaptic and particularly presynaptic proteins, neuronal or nuclear hypertrophy, changes in neuronal density and brain microstructure and others.

Risk factor for developing AD

In light of the role that mixed pathologies have, as well as the persistence of pathologies in the development of AD, it is important to consider the risk factors involved in these processes. In principle, risk factors may affect AD-pathology, vascular or other pathologies, modulate the interaction between them or be related to yet unknown pathologies.

We will list some factors other than genetics that also seem to influence the development of AD.

One such group is sociodemographic and behavioral factors. Education belongs to them. It has long been assumed that higher education slows the development of cognitive deficits. Multiple studies have shown the relationship between education and the degree of cognitive deficit independent of the degree of AD-pathology [8, 10, 26]. None of these studies show a direct relationship between education and the development of AD-pathology. It is believed that its positive role is carried out by improving the resistance of the brain against pathologies and building neuronal reserve capacity. This capacity may be expressed in the greater plasticity of the brain and the ability to more easily build compensatory connections at the site of the affected ones.

The group of sociodemographic and behavioural factors also includes physical, cognitive and social activities. Maintaining these activities is associated with a reduced risk of developing dementia [31, 32]. They can exert their positive effect through mechanisms such as improving the cardiovascular condition, as well as building reserve capacity by stimulating cognitive functions. Reading, solving crosswords, and participating in various games reduce the risk of dementia of the Alzheimer's type [30] and help preserve the plasticity of the brain. This is probably done through the same mechanisms that are influenced by education.

Increasing attention is being paid to the influence of nutrition and different diets on the risk of developing dementia. There is also a relationship between sleep and circadian rhythm with the dynamics of Aβ accumulation, and here the relationship is probably bidirectional – sleep helps to eliminate Aβ, and Aβ accumulation can lead to sleep disorders [17].

There are also psychological risk factors. According to Boyle et al. (2012) [5], people who have a purpose in life show fewer cognitive deficits, while depressive symptomatology contributes to cognitive impairment [32].

There are, of course, medical risk factors as well. Among them, the primary ones are cardiovascular, and their relationship with the risk of developing cerebrovascular disease and vascular dementia is well documented. Trauma of the head can be placed second. There are numerous studies on the relationship between traumatic brain injury and the increased risk of dementia [15]. There is no clear evidence whether AD is a direct pathological consequence or whether other neurodegenerative processes, such as chronic traumatic encephalopathy, are involved. Research results on the relationship between traumatic brain injury and Aβ deposition are conflicting.

Conclusions

It is clear from the above that dementias can have complex causes and their treatment must be complex [24]. In addition, AD is a multifunctional disease and the counteraction against it cannot be limited in only one direction. More and more systems in the brain are being discovered that are affected by the occurrence of AD. Many model systems have been used to study AD [19] but they have a number of limitations [20]. Due to its asymptomatic development for perhaps tens of years, it is particularly important to look for early markers to detect the pathological processes. The lack of clarity about the exact mechanisms causing AD as well as its long course means that therapy should also be very long-term and continue into old age. This, on one hand, places a heavy burden on public resources. On the other hand, medical treatment of the elderly can be problematic due to age-related changes in the kidneys and liver. Therefore, the main goal of research and the fight against AD should be its prevention. This can start now with improved control of cardiovascular risk factors, improved education and increased public information about the major risk factors.

At the same time, in-depth studies of the biochemical basis of Alzheimer's disease must continue in order to clarify its etiology in detail.

References

1. **Arnold, S. E., N. Louneva, K. Cao, L. S. Wang, L. Y. Han, D. A. Wolk, S. Negash, S. E. Leurgans, J. A. Schneider, A. S. Buchman, R. S. Wilson, D. A. Bennett**. Cellular, synaptic, and biochemical features of resilient cognition in Alzheimer's disease. – *Neurobiol. Aging*, **34**(1), 2013, 157-168.
2. **Azarpazhooh, M. R., A. Avan, L. E. Cipriano, D. G. Munoz, L. A. Sposato, V. Hachinski.** Concomitant vascular and neurodegenerative pathologies double the risk of dementia. – *Alzheimer's Dement.*, **14**, 2018, 148-156.
3. **Bennett, D. A.** Mixed pathologies and neural reserve: implications of complexity for Alzheimer disease drug discovery. – *PLOS Med***., 14,** 2017, e1002256.
4. **Bennett, D. A., R. S. Wilson, P. A. Boyle, A. S. Buchman, J. A. Schneider.** Relation of neuropathology to cognition in persons without cognitive impairment**.** – *Ann. Neurol***., 72,** 2012, 599-609.
5. **Boyle, P. A., A. S. Buchman, R. S. Wilson, L. Yu, J. A. Schneider, D. A. Bennett.** Effect of purpose in life on the relation between Alzheimer disease pathologic changes on cognitive function in advanced age. – *Arch. Gen. Psychiatry*, **69**, 2012, 499-504.
6. **Boyle, P. A., R. S. Wilson, L.Yu, A. M. Barr, W. G. Honer, J. A. Schneider, D. A. Bennett.** Much of late life cognitive decline is not due to common neurodegenerative pathologies. – *Ann. Neurol*., **74**, 2013, 478-489.
7. **Boyle, P. A., L. Yu, R. S. Wilson, S. E. Leurgans, J. A. Schneider, D. A. Bennett**. Person-specific contribution of neuropathologies to cognitive loss in old age. – *Ann. Neurol.*, **83**, 2018, 74-83.
8. **Brayne, C., P. G. Ince, H. A. Keage, I. G. McKeith, F. E. Matthews, T. Polvikoski T., R. Sulkava**. Education, the brain and dementia: neuroprotection or compensation? – *Brain*, **133**(Pt 8), 2010, 2210-2216.
9. **Brown, W. R., C. R. Thore**. Review: Cerebral microvascular pathology in ageing and neurodegeneration. – *Neuropathol. Appl. Neurobiol.,* **37**, 2012, 56-74.
10. **Farfel, J. M., R. Nitrini, C. K. Suemoto, L. T. Grinberg, R. E. Ferretti, R. E. Leite, E. Tampellini, L. Lima, D. S. Farias, R. C. Neves, R. D. Rodriguez, P. R. Menezes, F.**

Fregni, D. A. Bennett, C. A. Pasqualucci, W. Jacob Filho. Brazilian Aging Brain Study Group. Very low levels of education and cognitive reserve: a clinicopathologic study. – *Neurology*, **81**(7), 2013, 650-657.

11. Forrest, S. L., G. G. Kovacs. Current Concepts of Mixed Pathologies in Neurodegenerative Diseases. – *Canadian J. Neurological Sci*., **50**(3), 2023, 329-345,

12. Iturria-Medina, Y., R. C. Sotero, P. J. Toussaint, J. M. Mateos-Pérez, A. C. Evans. The Alzheimer's disease neuroimaging initiative. Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. – *Nat. Commun*., **7**, 2016, 11934

13. Jack, C. R. Jr., D. A. Bennett, K. Blennow, M. C. Carrillo, B. Dunn, S. B. Haeberlein, D. M. Holtzman, W. Jagust, F. Jessen, J. Karlawish, E. Liu, J. L. Molinuevo, T. Montine, C. Phelps, K. P. Rankin, C. C. Rowe, P. Scheltens, E. Siemers, H. M. Snyder, R. Sperling, Contributors. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. – *Alzheimer's Dement.*, **14**, 2018, 535-562.

14. James, B. D., D. A. Bennett, P. A. Boyle, S. Leurgans, J. A. Schneider. Dementia from Alzheimer disease and mixed pathologies in the oldest old. – *JAMA*, **307**, 2012, 1798-1800.

15. Jellinger, K. A. Head injury and dementia. – *Curr. Opin. Neurol.,* **17**, 2004, 719-723.

16. Joachim, C. L., J. H. Morris, D. J. Selkoe. Clinically diagnosed Alzheimer's disease: autopsy results in 150 cases. – *Ann. Neurol.,* **24**(1), 1988, 50-56.

17. Ju, Y.-E., B. P. Lucey, D. M. Holtzman. Sleep and Alzheimer disease pathology—a bidirectional relationship. – *Nat. Rev. Neurol.*, **10**, 2014, 115-119.

18. Kapasi, A., C. DeCarli, J. A. Schneider. Impact of multiple pathologies on the threshold for clinically overt dementia. – *Acta Neuropathol.,* **134**, 2017, 171-186.

19. Kirazov, L., E. Kirazov, C. Naydenov, V. Mitev. Model systems and approaches to the study of the metabolism of Alzheimer's amyloid precursor protein. – *Acta Morphol. Anthropol.,* **21**, 2015, 55-61.

20. Korczyn, A. D. The amyloid cascade hypothesis. – *Alzheimers Dement*., **4**(3)**,** 2008, 176-178.

21. Matthews, F. E., C. Brayne, J. Lowe, I. McKeith, S. B. Wharton, P. Ince. Epidemiological pathology of dementia: attributable-risks at death in the Medical Research Council Cognitive Function and Ageing Study. – *PLOS Med.*, **6**, 2009, e1000180.

22. Miyakawa, T. Vascular pathology in Alzheimer's disease. – *Psychogeriatrics,* **10**(1), 2010, 39-44.

23. Morrone, C . D., J. Bishay, J. A. McLaurin J. A. Potential role of venular amyloid in Alzheimer's disease pathogenesis. – *Int. J. Mol. Sci*., **21**(6), 2020, 1985.

24. Nichols, E., R. Merrick, H. I. Simon, D. Himali, J. J. Himali, S. Hunter, H. A. D. Keage, C. S. Latimer, M. R. Scott, J. D. Steinmetz, J. M. Walker, S. B. Wharton, C. D. Wiedner, P. K. Crane, C. D. Keene, L. J. Launer, F. E. Matthews, J. Schneider, S. Seshadri, L. White, C. Brayne, T. Vos. The prevalence, correlation, and co-occurrence of neuropathology in old age: harmonisation of 12 measures across six community-based autopsy studies of dementia. – *The Lancet,* **4**(3), 2023, E115-E125.

25. Robinson, J. L., X. X. Sharon, D. R. Baer, E.-R. Suh, V. M. Van Deerlin, N. J. Loh, D. J. Irwin, C. T. McMillan, D. A. Wolk, A. C. Plotkin, D. Weintraub, T. Schuck, V. M. Y. Lee, J. Q. Trojanowski, E. B. Lee. Pathological combinations in neurodegenerative disease are heterogeneous and disease-associated. – *Brain*, **146**(6), 2023, 2557–2569.

26. Roe, C .M., C. Xiong, J. P. Miller, N. J. Cairns, J. C. Morris. Interaction of neuritic plaques and education predicts dementia. – *Alzheimer Dis. Assoc. Disord*., **22**, 2008, 188-193.

27. Schneider, J. A., Z. Arvanitakis, W. Bang, D. A. Bennett. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. – *Neurology*, **69**, 2007, 2197-2204.

28. Tosun, D., O. Yardibi, T. L. S. Benzinger, W. A. Kukull, C. L. Masters, R. J. Perrin, M. W. Weiner, A. Simen, A. J. Schwarz. Identifying individuals with non-Alzheimer's disease co-pathologies: A precision medicine approach to clinical trials in sporadic Alzheimer's disease. – *Alzheimer's and Dementia*, **20**(1), 2024, 421-436.

29. Twait, L. E., L. Gerritsen, J. E. F. Moonen, I. M. W. Verberk,; C. E. Teunissen, P. J. Visser, W. M. van der Flier, M. I. Geerlings, UCC SMART Study Group, the NCDC Consortium. Plasma markers of Alzheimer's disease pathology, neuronal injury, and astrocytic activation and MRI load of vascular pathology and neurodegeneration: The SMART-MR study. – *Journal of the American Heart Association,* **13**(4), 2024

30. Valenzuela, M., C. Brayne, P. Sachdev, G. Wilcock, F. Matthews. Medical Research Council. Cognitive function and ageing study. Cognitive lifestyle and long-term risk of dementia and survival after diagnosis in a multicenter population-based cohort. – *Am. J. Epidemiol.* , **173(9)**, 2011, 1004-1012.

31. van der Flier, W. M., M. E. de Vugt, E. M. A. Smets et al. Towards a future where Alzheimer's disease pathology is stopped before the onset of dementia. – *Nat. Aging*, **3**, 2023, 494–505.

32. Wilson, R. S., A. W. Capuano, P. A. Boyle, G. M. Hoganson, L. P. Hizel, R. C. Shah, S. Nag, J. A. Schneider, S. E. Arnold, D. A. Bennett. Clinical-pathologic study of depressive symptoms and cognitive decline in old age. – *Neurology*, **83**(8)**,** 2014, 702-709.