MedCrave
Step into the World of Research

Journal of Neurology & Stroke

Perspective

Open Access

CrossMark

Brain capillaries in Alzheimer's disease

Volume 2 Issue 5 - 2015

Stavros J Baloyannis
Aristotelian University, Greece

Correspondence: Stavros J. Baloyannis, Aristotelian University, Angelaki 5, Thessaloniki 546 21 Hellas, Greece, Tel 302310270434, Fax 302310434, Email drnizamifurqan@yahoo.com

Received: August 21, 2015 | **Published:** September 08, 2015

Keywords: Alzheimer's disease, Brain capillaries, Blood brain barrier, Organelles, Electron microscopy

Abbreviations: AD, Alzheimer's disease; BBB, Blood Brain Barrier; EM, Electron microscopy; VaD, Vascular Dementia; VRFs, Vascular risk factors

Introduction

Alzheimer's disease is the most common cause of irreversible dementia, responsible for two-thirds of all the cases approximately, affecting mostly the presenile and senile age, shaping a tragic profile in the epilogue of the life of the suffering people.

Due to the severity of the disease and the gradually increased frequency of the patient worldwide, associated presumably with the increased aging of the populations, an ongoing research activity is in climax nowadays,[1] associated with many legal, social, ethical, humanitarian, philosophical and economic considerations.[2]

The clinical manifestations of the disease include gradual memory loss, disorientation, decline of speech fluency, loss of professional skills, behavioral disturbances, personality and emotional changes, learning disability, various neurologic deficits which appear increasingly as the disease advances.

From the neuropathological point of view the disease is characterized by dendritic pathology, loss of synapses and dendritic spines, affecting mostly selective neuronal networks of critical importance for memory and cognition, such as the basal forebrain cholinergic system, the medial temporal regions, the hippocampus and many neocortical association areas.[3] Tau pathology consisted of intracellular accumulation of neurofibrillary tangles of hyperphosphorilated tau protein and accumulation of Aβ-peptide's deposits, defined as neuritic plaques, are the principal neuropathological diagnostic criteria of the disease.[4]

The neurotoxic properties of the oligomerics of the Aβ-peptide and tau mediated neurodegeneration are among the main causative factors of impaired synaptic plasticity,[5] neuronal loss,[6] dendritic alterations,[7] and tremendous synaptic loss.[8] The gradual degeneration of the organelles, particularly mitochondria, smooth endoplasmic reticulum and Golgi Apparatus,[8] visualized clearly by electron microscopy, emphasize the importance of the oxidative stress and amyloid toxicity in shaping the fine folds of the etiopathological background, which is plotted many years prior to phenomenological appearance of the disease.

The vascular factor may be an important component of the spectrum of the pathogenesis of AD. First, it is essential that the concrete and sharp differentiation between AD and VaD has undergone critical reviews the last years, given that mixed findings at autopsy, plead in favor of a vascular component, concerning mostly large vessel, in AD pathology,[9] and second, that vascular comorbidity may be present in a substantial number of patients suffered from AD,[10,11] and furthermore VRFs, such as cardiovascular diseases,[12] hyperhomocysteinhemia, diabetes mellitus, obesity and hypertension may contribute in increasing the incidence of AD,[13] pansari in advanced ages.

It is of substantial importance the concept that the structural alterations of the brain capillaries, may contribute in the pathology of AD,[14] given that the disruption of the BBB[15] may induce exacerbation of AD pathology, by promoting inflammation around the blood capillaries and in the neuropile space diffusely. That phenomenon leads to the hypothesis that a primary vascular damage at the level of brain capillaries may increase the accumulation of Aβ-peptide in the brain in AD.[16] Alternatively, the disruption of the BBB, which is the main physical protection system of the brain, consisted of the tight junctions of the endothelial cells of the blood capillaries[17] and supported by astrocytes and pericytes, may be initiated by the toxic effects of oligomeric Aβ-peptide[18] or by the tau protein.[19] Tau protein may accumulate as puncta in perivascular spaces in sporadic AD[20] and tau alone can initiate breakdown of the BBB, which can recover integrity when tau levels are reduced.[19] Dysfunction of the brain capillaries may lead to Aβ-peptide increased accumulation in the brain, since brain hypoxia and hypometabolism are among the modulators of cerebral amyloidogenesis.[21]

Studies based on positron emission tomography have revealed regional metabolic decrease in patients suffered from MCI or possible AD,[22] which correlates directly with the dementia's rate.[23] In addition, in experimental research, disruption of BBB and dysfunction of the endothelial cells was described in Slit-2 overexpressing transgenic mice.[24]

The correlation between AD pathology and vascular pathology, at the level of brain capillaries and BBB, raises the rational question, whether the efficient treatment of the vascular factor might be beneficial for the patients who suffer from AD.[25,26] It is reasonable that any protection of the brain capillaries at the initial stages of the disease might contribute in the abbreviation of the long chain of pathological alteration, which occur following the disruption of the BBB, which serves as the essential interface between the vascular system and the brain.

From the morphological point of view, silver impregnation techniques revealed a marked tortuosity of the capillaries in the hippocampus and the cerebral cortex in early cased of AD.[14] In addition, the distance between two branch points is longer in capillaries of AD brains, whereas the branch point density as well as the ratio of the branch point density to astrocytic density is substantially decreased in AD in comparison with age matched normal controls.[14]

EM revealed, that the most frequent morphological alterations of the brain capillaries in AD consist of thickness, splitting and duplication of the basement membrane, reduction of the length of tight junctions, decrease of the number of tight junctions per vessel length, associated as a rule, with morphological alterations of the mitochondria of the endothelial cells, the pericytes and the perivascular astrocytic processes.[14]

The number of the pinocytotic vesicles is substantially increase in the endothelium of the brain capillaries in AD in comparison with age matched normal controls.[14] Endothelial cells play a very important role in the transport systems in the brain, mediating the delivery of glucose and amino-acids to the brain and contributing in the clearance of toxic metabolic factors from the brain to blood.[27] Subsequently, the dysfunction of the endothelial cells and the disruption of the BBB may induce serious impairment in the transport system of the brain.[28]

In a substantial number of cases of AD, degeneration of the pericytes is also observed emphasizing even more the importance of the vascular factor.[14] Pericytes share basement membrane with endothelial cells and come in contact with them cell to cell. In the capillaries of the CNS, the ratio between pericytes-to-endothelial cells is higher than in other parts of the body.[29] Pericytes may serve as integrators, coordinators and effectors of blood–brain barrier structure and maintenance, and play a key role in microvascular stability[30,31] capillary density and angiogenesis.[32] It is worth to underline that accelerated pericyte degeneration occur in AD APOE4 carriers,[33] the major genetic risk factor of AD, who also may demonstrate vascular permeability changes prior to cognitive decline.[34]

The dysfunction of the brain capillaries may result in releasing neurotoxic factors, such as thrombin,[35] pro-inflammatory cytokines, nitric oxide and leukocyte adhesion molecules,[36,37] and in abnormal regulation of Aβ-peptide homeostasis in the brain, which contribute substantially in the further pathogenetic steps of AD. The impairment of the brain capillaries in structures of the brain, which are crucial for the homeostatic equilibrium of the body, such as the hypothalamic nuclei,[38] may induce autonomic dysfunction, which usually occurs in the advanced stages of AD, affecting dramatically the viability of the patients.

The association of the VRFs with AD, and the frequent pathology of brain capillaries inducing the disruption of the BBB in AD may plead in favor of a focused strategy, aiming at protecting the brain capillaries, avoiding oxidative stress and any alteration of the pericytes and over most protecting the mitochondria, which may be beneficial in the initial stages of AD.

Acknowledgments

None.

Conflicts of interest

None.

References

1. World Health Organization (WHO). *Dementia*: a public health priority. World Health Organization, Geneva. 2012;pp.112.
2. Baloyannis S. The philosophy of dementia. *Encephalos*. 2010;47(3):109–130.
3. Jellinger K, Bancher C. Neuropathology of Alzheimer's disease: a critical update. *J Neural Transm Suppl*. 1998;54:77–95.
4. Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol.* 2012;123(1):1–11.
5. Shankar GM, Li S, Mehta TH, et al. Amyloid–beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nat Med*. 2008;14(8):837–842.
6. Ballatore C, Lee VM, Trojanowski JQ. Tau–mediated neurodegeneration in Alzheimer's disease and related disorders. *Nat Rev Neurosci*. 2007;8(9):663–672.
7. Baloyannis SJ. Dendritic pathology in Alzheimer's disease. *J Neurol Sci*. 2009;15(283):153–157.
8. Baloyannis SJ. Alterations of mitochondria and Golgi apparatus are related to synaptic pathology in Alzheimer's disease. In: Kishore U (Ed.), *Neurodegenerative Diseases*. InTech, Rijeka, Croatia. 2013;pp.101123.7.
9. Ligthart SA, Moll van Charante EP, Van Gool WA, et al. Treatment of cardiovascular risk factors to prevent cognitive decline and dementia: a systematic review. *Vasc Health Risk Manag*. 2010;6:775–785.
10. Jellinger KA, Attems J. Prevalence and pathogenic role of cerebrovascular lesions in Alzheimer disease. *J Neurol Sci*. 2005;229–230:37–41.
11. Jellinger KA, Attems J. The overlap between vascular disease and Alzheimer's disease – lessons from pathology. *BMC Med*. 2014;12:206.
12. de Bruijn RF, Ikram MA. Cardiovascular risk factors and future Alzheimer's disease risk. *BMC Med*. 2014;12: 130.
13. Pansari K, Gupta A, Thomas P. Alzheimer's disease and vascular factors: facts and theories. *Int J Clin Pract*. 2002;56(3):197–203.
14. Baloyannis SJ, Baloyannis IS. The vascular factor in Alzheimer's disease: a study in Golgi technique and electron microscopy. *J Neurol Sci*. 2012;322(1–2):117–121.
15. Marques F, Sousa JC, Sousa N, et al. Blood–brain–barriers in aging and in Alzheimer's disease. *Mol Neurodegener*. 2013;8:38.
16. Sagare AP, Bell RD, Zlokovic BV. Neurovascular dysfunction and faulty amyloid Aβ2–peptide clearance in Alzheimer disease. *Cold Spring Harb Perspect Med*. 2012;2(10):doi:10.1101/cshperspect.a011452.
17. Broadwell RD, Salcman M. Expanding the definition of the blood–brain barrier to protein. *Proc Natl Acad Sci U S A*. 1981;78(12):7820–7824.
18. Oshima K, Uchikado H, Dickson DW. Perivascular neuritic dystrophy associated with cerebral amyloid angiopathy in Alzheimer's disease. *Int J Clin Exp Pathol*. 2008;1(5):403–408.
19. Blair LJ, Frauen HD, Zhang B, et al. Tau depletion prevents progressive blood–brain barrier damage in a mouse model of tauopathy. *Acta Neuropathologica Communications*. 2015;3:8.
20. Vidal R, Calero M, Piccardo P, et al. Senile dementia associated with amyloid beta protein angiopathy and tau perivascular pathology but not neuritic plaques in patients homozygous for the APOE–epsilon4 allele. *Acta Neuropathol*. 2000;100(1):1–12.
21. Zhang X, Zhou K, Wang R, et al. Hypoxia–inducible factor 1alpha (HIF–1alpha)–mediated hypoxia increases BACE1 expression and beta–amyloid generation. *J Biol Chem*. 2007;282(15):10873–10880.
22. Sedaghat F, Dedousi E, Baloyannis I, et al. Brain SPECT findings of anosognosia in Alzheimer's disease. *J Alzheimers Dis*. 2010;21(2):641–647.
23. Rapoport S. Positron emission tomography in Alzheimer's disease in relation to disease pathogenesis: a critical review. *Cerebrovasc Brain Metab Rev*. 1991;3(4):297–335.
24. Li JC, Han L, Wen YX, et al. Increased Permeability of the Blood–Brain Barrier and Alzheimer's Disease–Like Alterations in Slit–2 Transgenic Mice. *J Alzheimer's Dis* .2015;43(2):535–548.

25. Valenti R, Pantoni L, Markus HS. Treatment of vascular risk factors in patients with a diagnosis of Alzheimer disease; a systematic review. *BMC Med*. 2014;12:160.

26. O'Brien JT, Markus HS. Vascular risk factors and Alzheimer's disease. *BMC Medicine*. 2014;12:218.

27. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci*. 2011;12(12):723–738.

28. Brown WR, Thore CR. Review: cerebral microvascular pathology in ageing and neurodegeneration. *Neuropathol Appl Neurobiol*. 2011;37(1):56–74.

29. Shepro D, Morel NM. Pericyte physiology. *FASEB J*. 1993;7(11):1031–1038.

30. Bell RD, Winkler EA, Sagare AP, et al. Pericytes control key neurovascular functions and neuronal phenotype in the adult brain and during brain aging. *Neuron*. 2010;68(3):409–427.

31. Bell RD, Winkler EA, Singh I, et al. Apolipoprotein E controls cerebrovascular integrity via cyclophilin A. *Nature*. 2012;485(7399):512–516.

32. Winkler EA, Sagare AP, Zlokovic BV. The pericyte: a forgotten cell type with important implications for Alzheimer's disease? *Brain Pathol*. 2014;24(4):371–386.

33. Halliday MR, Rege SV, Ma Q, et al. Accelerated pericyte degeneration and blood–brain barrier breakdown in apolipoprotein E4 carriers with Alzheimer's disease. *J Cereb Blood Flow Metab*. 2015;doi:10.1038/jcbfm.2015.44.

34. Halliday MR, Pomara N, Sagare AP, et al. Relationship between cyclophilin a levels and matrix metalloproteinase 9 activity in cerebrospinal fluid of cognitively normal apolipoprotein e4 carriers and blood–brain barrier breakdown. *JAMA Neurol*. 2013;70(9):1198–1200.

35. Yin X, Wright J, Wall T, et al. Brain endothelial cells synthesize neurotoxic thrombin in Alzheimer's disease. *Am J Pathol*. 2010;176(4):1600–1606.

36. Grammas P. Neurovascular dysfunction, inflammation and endothelial activation: implications for the pathogenesis of Alzheimer's disease. *J Neuroinflammation*. 2011;8:26.

37. Lyros E, Bakogiannis C, Liu Y, et al. Molecular links between endothelial dysfunction and neurodegeneration in Alzheimer's disease. *Curr Alzheimer Res*. 2014;11(1):18–26.

38. Baloyannis SJ, Mavroudis I, Mitilineos D, et al. The hypothalamus in Alzheimer's disease: a golgi and electron microscope study. *Am J Alzheimers Dis Other Demen*. 2015;30(5):478–487.