Exploratory Research and Hypothesis in Medicine **2024** vol. 9(3) | 258–260
DOI: 10.14218/ERHM.2023.00080

Opinion

Cerebral Small Vessel Disease in Neurodegenerative Lesions

Ivan V. Maksimovich*

Clinic of Cardiovascular Diseases named after Most Holy John Tobolsky, Moscow, Russia

Received: August 15, 2023 | **Revised:** September 20, 2023 | **Accepted:** November 15, 2023 | **Published online:** December 18, 2023

The lifespan in economically developed countries is increasing while the birth rate is declining, resulting in population aging. This is leading to a growing number of cerebral ischemic and neurodegenerative lesions.[1]

Physiologically, the brain is the most actively blood-supplied organ and has its own features of angioarchitectonics and hemodynamics. It has the most powerful microcirculatory network: 1 cubic centimeter of cerebral tissue contains 3 to 4 thousand capillaries. Even minor microcirculation disorders lead to decreased hemodynamics and the development of hypoperfusion, hypoxia, neurodegeneration, and ischemia.[2] Let us consider the most common cases.

Alzheimer's disease (AD) has become widespread nowadays. This is a neurodegenerative disease that leads to cerebral atrophy, dementia development, and mental and cognitive disorders, greatly complicating the lives of patients and their relatives.[1,3–7]

AD occupies the leading position among neurodegenerative diseases. Considering all dementia cases, 60–80% are related to AD. It begins to develop at an early age, many years before primary clinical manifestations. This period is described as the preclinical AD stage.[3–8] However, researchers prefer to look at older patients with more advanced stages of AD. In 2023, in the USA, 6.7 million people aged 65+ had AD. During the study, younger patients were not considered; therefore, the true number of patients is much higher. There is an opinion that by 2060, the number of USA patients with AD may exceed 13 million. Moreover, mortality from AD is progressively increasing.[1]

Worldwide, the number of AD patients registered is about 32 million. Simultaneously, patients with preclinical AD who do not present clear complaints and do not go to medical institutions can make up 300 million.[4–7]

Despite numerous long-term studies, etiological and pathogenetic AD factors still need to be fully understood. Regarding AD development, it must be considered that it occurs not only as a result of amyloid beta (Aβ) and tau-protein metabolism disorders in the cerebral tissue but also as a result of disorders in cerebral angioachitectonics and microcirculation, manifesting with a specific lesion-cerebral small vessel disease (CSVD).[3,7] These vascular and microvascular changes are called "dyscirculatory angiopathy of Alzheimer's type" (DAAT).[7]

DAAT is not related to the development of atherosclerotic cerebral lesions.[7] In AD, increased tortuosity develops in the distal intracerebral arteries. In the hippocampus and temporal regions, capillaries are reduced, their number and branching decrease, and they become thinner, leading to hypovascular zone development. A similar process occurs in frontoparietal regions, where hypovascular zones also develop. Capillary blood flow is restructured in the brain, leading to hemodynamic disorders. Arterial blood cannot pass through the reduced capillaries, which causes decreased distal arterial blood flow. In the temporal and frontoparietal regions, arteriovenous shunts open, through which arterial blood, bypassing the capillaries, enters the venous bed. The volumetric inflow of arterial blood into the venous bed leads to its overflow, venous outflow disruption, and blood stasis. Consequently, large pathologically dilated venous trunks develop. Because of these changes, the cerebral hemodynamics are completely restructured and chronic hypoperfusion and hypoxia develop.[3,7]

With natural aging and other neurodegenerative and ischemic cerebral lesions, there are no such changes in arterial, capillary, and venous beds.[7]

Cerebral hypoperfusion and hypoxia developed during AD impair adenosine triphosphate metabolism and cause mitochondria death in the smooth endoplasmic reticulum and the Golgi apparatus cells, destroying synapses and causing neuron degeneration and death.[7–9] Consequently, the neurovascular unit is damaged.[7]

Decreased cerebral capillary blood flow and hemodynamic disorders affect Aβ metabolism, leading to decreased natural excretion and increased accumulation. Developed pathological changes lead to Aβ deposition in the cerebral tissue and vascular wall. Simultaneously, natural physiological intracerebral angiogenesis decreases and blood-brain barrier disorders develop.[7]

All these pathological changes are inextricably linked. During their development, they exacerbate each other and cause cerebral dysfunction and neurodegeneration.[7,8]

The degree of atrophic changes in AD is determined by the tomography dementia rating scale (TDR). DAAT is detected in all stages of AD, from its preclinical stage TDR-0, with no expressed dementia or cognitive deficits, to mild stages of TDR-1, moderately severe TDR-2 and severe TDR-3 stages.[7]

Similar cerebrovascular changes can be found in the direct AD patients' descendants at their early age, indicating that these changes in cerebral angioarchitectonics are genetically determined and of hereditary character.[7] Recent studies have shown that 30 of 45 major genes associated with the risk of AD developing are

Keywords: Alzheimer's disease; Cerebral small vessel disease; Microcirculation disturbance; Tomography dementia rating scale.

***Correspondence to:** Ivan V. Maksimovich, Clinic of Cardiovascular Diseases named after Most Holy John Tobolsky, Building 2, Block 15, 6th Lazenki Str., 119619 Moscow, Russia. ORCID: https://orcid.org/0000-0002-8640-4182. Tel: +7-903-7240 277, Fax: +7-495-4390945, E-mail: carvasc@yandex.ru

How to cite this article: Maksimovich IV. Cerebral Small Vessel Disease in Neurodegenerative Lesions. *Explor Res Hypothesis Med* 2024;9(3):258–260. doi: 10.14218/ERHM.2023.00080.

located in the intracerebral vasculature, which indicates the genetic nature of cerebrovascular changes in AD.[8]

The more pronounced cerebral hypoperfusion and hypoxia caused by DAAT are, the more actively Aβ accumulates and the faster AD develops.[7,8] The mechanisms leading to gradual AD development are being ascertained nowadays. These slow processes determine the period the patient passes from preclinical AD to its clinical stages.[7]

Another extremely common cause leading to impaired cerebral blood supply and hemodynamics is atherosclerosis. Its development is a rather complex process. In one way of its development, atherosclerosis predominantly affects proximal intracerebral arterial branches. In these fairly large arteries, stenotic lesions develop, causing lumen narrowing, reduced blood flow, hypoxia development, and long-term chronic cerebrovascular insufficiency.[7]

Slowly developing hypoxia and ischemia stimulate brain angiogenesis, causing collateral arterial and capillary bed development. Collateral vessels allow blood to be delivered to ischemic areas from other vascular pools.[3,7]

Atherosclerosis progression leads to the development of occlusive lesions of intracerebral vessels. Blood flow along this branch stops completely, leading to ischemic stroke development. Ischemic stroke can occur in both white and gray cerebral matter.

In elderly patients with long-term chronic cerebrovascular insufficiency and developed collateral blood supply, stroke is milder than in young patients with undeveloped collateral blood supply.[7]

In another way of cerebral atherosclerosis development, disseminated damage of small arterial branches and capillaries occurs, which causes the development of CSVD of atherosclerotic etiology. Gradually increasing hypoxia disrupts adenosine triphosphate metabolism in neuronal mitochondria, leading to the death of individual cells and their groups. Transient attacks and lacunar microstrokes accompany this process. Consequently, multiple foci of neurodegeneration and gliosis slowly develop in the corresponding brain parts.[2,3,7]

With the predominance of the process at the subcortical level, depending on the location of atherosclerotic lesions in one or another part of the white cerebral matter, there is gradual development of Binswanger's disease (BD) or vascular Parkinsonism (VP).[10]

BD develops in old age. Recently, the number of patients suffering from it has increased. BD now reaches 30% of all dementia types. BD etiology still needs to be fully understood. It is often associated with cerebral hypertension. During BD, CSVD develops, which is completely different from the changes developing in AD.[3,10]

CSVD in BD subcortically disseminatedly affects brain white matter. These changes are atherosclerotic and manifest by subcortical lesions of small arterial branches, arterioles, and capillaries.[7,10] This specific microvascular lesion affects the cerebral venous system less than in AD. As a result, small subcortical arteriovenous shunts develop in the cerebral white matter, not leading to venous stasis.[10]

In BD, the slowly developing subcortical CSVD leads to progressive hypoxia, ischemia, and subcortical neuron death. First, individual neurons die, then their groups. At the initial stages of BD development, disseminated cerebral gliosis foci are small and can often be invisible on computed tomography and magnetic resonance imaging.[7,10] Developing ischemia may be accompanied by transient attacks and lacunar microstrokes. Simultaneously, microstrokes can occur without pronounced clinical symptoms. As BD progresses, the neurodegeneration foci coalesce and form widespread gliosis. With further BD progression, patients develop leukoareosis phenomena. Widespread subcortical demyelization in BD leads to cerebral degeneration and atrophy. Clinically, this is manifested by dementia development, cognitive, mental, and motor disorders, and decreased daily life activities, greatly complicating the life of patients and their relatives.[10]

VP develops in old age. Its etiology and pathogenesis still need to be fully understood. In VP, CSVD has an atherosclerotic etiology and develops at the subcortical level with the involvement of cerebral white matter. In contrast to the disseminated microvascular lesion in BD, CSVD in VP is local in nature and it is found in the thalamus, basal ganglia, and pons.[10] Accordingly, neurodegeneration and gliosis foci are usually located in the same regions. Because of their small size in the early stages, gliosis foci may be hardly noticeable during computed tomography and magnetic resonance imaging. With VP development, it can also be accompanied by transient attacks and microstrokes without pronounced clinical symptoms. Atrophic cerebral VP changes are less pronounced than in other neurodegenerative lesions. Clinically, in VP, the corresponding motor impairments are more pronounced. However, mental cognitive disorders and dementia can also be present, but they are usually milder than in BD.[10]

BD and VP have much in common, both resulting from CSVD with atherosclerotic lesions of subcortical intracerebral arterioles and capillaries. The difference is that there is widespread disseminated neurodegeneration with leukoareosis development in BD, while in VP, local neurodegeneration occurs.

CSVD in neurodegenerative cerebral lesions has different times of occurrence, etiology, localization, and prevalence. Nevertheless, in all cases, CSVD data contribute to or cause the development of cerebral neurodegeneration with the subsequent development of the corresponding disease.

Microvascular disorders, which develop in the brain as a result of traumatic brain injury, make up a separate group. Traumatic brain injury is not a neurodegenerative disorder. However, the external impact on the brain leads to damage in both cerebral tissue and microvascular bed, which is the primary damage. The resulting changes contribute to the development of secondary cerebrovascular disorders. Taken together, these changes lead to subsequent cerebral neurodegeneration and the development of cognitive deficits.[11]

Timely CSVD detection in cerebral neurodegenerative lesions is essential for establishing the correct diagnosis and treatment choice.

Acknowledgments

There is nothing to declare.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest

The author declares that there is no conflict of interest.

Author contributions

IVN is the sole author of the article.

References

[1] Alzheimer's disease facts and figures. Alzheimers Dement 2023;19(4):1598–1695. doi:10.1002/alz.13016, PMID:36918389.

[2] Gjulev NM, Pustozertsev VG, Gjulev SN. Cerebrovascular Diseases 2002;MoscowNevsky Dialect.
[3] Cai Z, Wang C, He W, Tu H, Tang Z, Xiao M, *et al*. Cerebral small vessel disease and Alzheimer's disease. Clin Interv Aging 2015;10:1695–1704. doi:10.2147/CIA.S90871, PMID:26604717.
[4] Henein M, Arsenault-Lapierre G, Sourial N, Godard-Sebillotte C, Bergman H, Vedel I, *et al*. Description of organizational and clinician characteristics of primary dementia care in Canada: a multi-method study. BMC Prim Care 2022;23(1):121. doi:10.1186/s12875-022-01732-9, PMID:35590272.
[5] van der Flier WM, de Vugt ME, Smets EMA, Blom M, Teunissen CE. Towards a future where Alzheimer's disease pathology is stopped before the onset of dementia. Nat Aging 2023;3(5):494–505. doi:10.1038/s43587-023-00404-2, PMID:37202515.
[6] Rafii MS, Aisen PS. Detection and treatment of Alzheimer's disease in its preclinical stage. Nat Aging 2023;3(5):520–531. doi:10.1038/s43587-023-00410-4, PMID:37202518.
[7] Maksimovich IV. Differences in cerebral angioarchitectonics in Alzheimer's disease in comparison with other neurodegenerative and ischemic lesions. World J Neurosci 2018;8(4):454–469. doi:10.4236/wjns.2018.84036.
[8] Yang AC, Vest RT, Kern F, Lee DP, Agam M, Maat CA, *et al*. A human brain vascular atlas reveals diverse mediators of Alzheimer's risk. Nature 2022;603(7903):885–892. doi:10.1038/s41586-021-04369-3, PMID:35165441.
[9] Baloyannis SJ. Brain capillaries in Alzheimer's disease. Hell J Nucl Med 2015;18(Suppl 1):152. doi:10.15406/jnsk.2015.02.00069.
[10] Maksimovich IV. Intracerebral transcatheter laser photobiomodulation therapy in the treatment of binswanger's disease and vascular parkinsonism: research and clinical experience. Photobiomodul Photomed Laser Surg 2019;37(10):606–614. doi:10.1089/photob.2019.4649, PMID:31390288.
[11] Logsdon AF, Lucke-Wold BP, Turner RC, Huber JD, Rosen CL, Simpkins JW. Role of microvascular disruption in brain damage from traumatic brain injury. Compr Physiol 2015;5(3):1147–1160. doi:10.1002/cphy.c140057, PMID:26140712.