REVIEWS

Research progress on risk factors for leukoaraiosis

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Abstract

Leukoaraiosis (LA), a term of neural imaging, is a disease which clinically causes cognitive dysfunction and gait disorders, eventually leads to persistent or progressive cognitive and neural dysfunction, seriously affects patients' daily lives. Early detection and identification of LA and its risk factors and early intervention may be of help to improve the quality of patients' living in the future. The research progress on risk factors for LA was reviewed in this study.

Key Words: Leukoaraiosis, Risk factors, Research progress

Leukoaraiosis (LA), a neuroimaging term first proposed by Canadian neurologist Hachinski in 1987, is used to describe speckled and patchy changes in appearance of white matter near the lateral ventricles and/or subcortex (centrum semiovale). CT manifestation shows PVLD; MRI shows isointense and/or hypointense of T1WI, hyperintense of T2WI and hyperintense of FLAIR. At present, with the extensive application of CT and MRI, the detection rate of LA is significantly increased. By disrupting signal transduction between neurons as well as between cortex and subcortical centrum, white matter damage causes cognitive dysfunction and gait disorders, and ultimately is showed as persistent or progressive cognitive and neurological dysfunction. Therefore, the family and the society bear an increasingly heavier burden. Currently, as there is no specific treatment for LA, the prevention of LA becomes essential gradually. The research progress on risk factors for LA is reviewed in the sections below.

1 Age

Nearly all researches suggest that age is an independent risk factor for LA. LA is an imaging change common in elderly patients; detection rates of patients over 60 years by CT and MRI were as high as 7%-30% and 8%-100% respectively.[1] Besides, the incidence of LA is gradually increased with age.[2] The research made by Peng CY et al.[3] shows that age is an independent risk factor for LA, but the severity of LA is not associated with age. In current researches, there is no precise data concerning the focus scope of LA in a particular age, i.e., research results cannot clarify that at what age LA starts to progress.

As to the role of age in LA, firstly, intracerebral proteins such as myelin basic proteins and lecithins are main components of myelin. The number of those proteins is increased with age at birth and decreased gradually after being an adult. Most of nerve fibers in white matter are myelinated fibers. Therefore, demyelination changes come with age eventually. Secondly, what comes with age as well is cerebral arteriolar sclerosing vascular change. When the blood pressure is decreased, these sclerosing blood vessels cannot maintain the blood supply in brain white matter by way of vasodilation, and then cerebral white matter chronic ischemia arises eventually.[4]

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2 Gender

Some scholars at home and abroad[5,6] have found that females may be more prone to LA than males. The probable cause is the change in the level of estrogens. The decrease of estrogen level in postmenopausal females will cause ischemia-hypoxia in brain white matter and then lead to LA eventually; Sijens et al.[7] consider that ratios and metabolite concentrations of choline, creatinine and N-acetylaspartate in front area near the lateral ventricles in females are all higher than those in males. This is probably a cause of the occurrence and development of LA. The factors that cause the difference in gender have not been identified yet. Nevertheless, some scholars[4,8] have researched and failed to verify that females may be more prone to LA than males. Therefore, the current conclusions on the relevance of gender to LA are still controversial, and it is necessary to make a further study, exploration and verification.

3 Blood pressure

Currently, most of researches suggest that hypertension is one of risk factors that cause LA.[3–5,9–11]

Meng XJ et al.[5] consider that hypertension history, especially high diastolic blood pressure, is an independent risk factor for LA. Ren J et al.[10] find that abnormal day-to-night variation rhythm of blood pressure has an effect on the incidence of LA. Foreign studies have found that both systolic and diastolic blood pressures are associated with severe periventricular white matter lesions. Compared with patients with well-controlled blood pressure, patients with badly-controlled blood pressure may be at a higher risk for suffering white matter lesions. To control hypertension successfully can reduce this risk.[11] The research made by Peng CY et al.[3] have shown that the severity of LA is not associated with the course of hypertension although it is an independent risk factor for LA.

Long-term hypertension can cause inner-wall thickening and hyalinization of intracranial arteriolae and deep perforating arteries with luminal stenosis. When the blood pressure is decreased, it easily leads to low perfusion in white matter and then gives rise to LA.[12] At the same time, atherosclerosis or aneurysm and microthrombus can be formed in blood vessels due to luminal stenosis, and lead to decreased blood supply, cerebral ischemia and hypoxia demyelination[13] which can cause LA. In addition, hypertension can also cause changes in vascular permeability and damages of blood-cerebrospinal fluid barrier, leading to cerebral edema, astrocyte activation, and white matter damage caused by the penetration of destructive enzymes and other injurious toxic substances.[12]

However, there are some different views in a few studies as well. For example, Robert[14] considers that, LA is related to the status of hypotension. Tarvone-Schroder et al.[15] also propose that cerebral hypoperfusion caused by hypotension may be the main reason for LA.

Therefore, opinions on the relationship between blood pressure and LA have not been completely unified yet and still remain to be further studied.

4 Hyperhomocysteinemia

Homocysteine (HCY) is a type of sulfur-containing amino acids. It is an important intermediate product in the metabolic process of methionine which is an amino acid needed for human body, and an amino acid that can damage blood vessels.

Current studies have shown that high level of HCY in plasma is a risk factor for LA.[9,16–22] For example, scholars at home and abroad have found that[9,16,17] LA is positively correlated to hyperhomocysteinemia. Pavlovic et al.[18] have also found that, the level of HCY in plasma is significantly higher in patients with cerebral small vessel diseases than that in healthy subjects, and it is positively correlated to the severity of white matter lesions. Therefore, HYC can be considered as an independent predictive factor for LA. A domestic research[19] suggests that hyperhomocysteinemia has no significant association with cerebral large vessel diseases, but it is an independent risk factor for LA. A research in New Zealand[20] shows that high level of HCY in plasma and hyperhomocysteinemia are significantly associated with the volume of LA.

Effects of high level of HCY on white matter and its role are as follows: High level of HCY is related to the occurrence of cerebral microvascular diseases.[21] It results in intracerebral arteriolar atherosclerosis (caused by oxidative stress, platelet activation and other mechanisms), white matter ischemia damage and formation of LA by affecting vascular endothelial function, damaging cerebrovascular endothelial cells, promoting proliferation of vascular smooth muscle cells, affecting lipid metabolism and peroxidation reaction.[16] In addition, HCY is a marker of hypomethylation. Increased HCY concentration will affect the integrity of myelin sheaths, that is, HCY is an antagonist of N-methyl-D-aspartate and has a directly neurotoxic effect on myelin sheaths, and will cause myelinated degeneration and demyelination.[22]

However, there are also some studies showing that it is no significant correlation between them. For example, Quadri et al.[23] have found that LA has no obvious relationship with hyperhomocysteinemia. Turaj et al.[24] have found that the level of HCY in plasma in patients with cerebal small vessel diseases is not higher than that in healthy subjects, which indicates that there is no relationship between the two factors.

Therefore, current research conclusions on the relevance of hyperhomocysteinemia to LA have not been completely unified yet and still remain to be further studied and verified.

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5 Diabetes

Most of current findings have provided a supporting evidence for the relevance of diabetes and LA.[8,25–27]

Findings from Gouw AA's research[25] have shown that, diabetes is associated with the progress of LA. Results from Qi D et al.'s study[26] have indicated that the ratio of patients with glycometabolism abnormality and the level of blood glucose in LA group are significantly higher than those in non-LA group. Glycometabolism abnormality is significantly related to the severity of LA. In a research from South Korea,[27] it is found that diabetes is independently associated with LA and considered as a determinant of microvascular complications of LA.

High blood glucose can accelerate the occurrence of atherosclerosis with obviously increased severity. Multiple intracranial and extracranial vascular stenosis can often happen to diabetic patients with seriously affected cerebral hemodynamics and declined vascular reactivity and vascular auto-regulation, which contribute to the increase in the incidence of LA.

However, not all studies come to an affirmed conclusion.[3,28] Peng CY et al.[3] conduct a retrospective survey on patients with LA and find that, patients with a history of diabetes are faced with less risk of LA. The probable reason is that long-term diet control and oral hypoglycemic agents for diabetic patients have a preventive effect on the occurrence of LA; it is also probable that, differed from common cerebrovascular diseases, the incidence of LA is of its own characteristics; besides, it is unable to identify the relevance of IGT history to the occurrence of LA. Kim et al.[28] have found that diabetes can only increase the incidence of macrovascular diseases, with no significant increase in the incidence of microvascular diseases. Therefore, it is speculated that diabetes probably has no direct relationship with LA.

All in all, conclusions that diabetes is a risk factor for LA are still controversial, and it is necessary to make a further study, exploration and verification.

6 Blood lipid

A number of studies have shown that hyperlipoidemia is a risk factor for the occurrence of LA, and the severity of LA is associated with hyperlipoidemia.[29–31]

In many researches, increased levels of cholesterols, triglycerides and low-density lipoproteins (LDLs) are thought to be associated with the occurrence of LA.[29,30] Yin Y et al.[30] also find that overall levels of cholesterols and LDLs are related to the degree of LA, and triglycerides have no relationship with the degree of LA. Some scholars have found that apolipoprotein B is a risk factor for white matter damage, while apolipoprotein A is a protective factor.[31]

Hyperlipoidemia and abnormal lipoprotein metabolism are closely related to atherosclerosis. These two factors not only promote the formation of cerebral atherosclerosis and regional plaques, accelerate endovascular stenosis, slow down the blood flow, but also cause white matter ischemia and dysfunction through ischemia and hypoxia caused by cerebral atherosclerosis, so that the risk of LA is subsequently increased.

On the other hand, the results acquired by some scholars do not support the above-mentioned view.[4,5] Meng XJ et al.[5] find that the increase in total cholesterol can reduce the risk of LA. This may be related to the difference in pathogenesis mechanisms of LA and large-artery atherosclerosis, the former is mainly due to arteriolar hyalinization.[32] There are also some researches[33] indicating that in comparison with cerebral small vessel diseases, carotid atherosclerosis is more closely related to hypercholesterolemia; high low-density lipoproteinemia is an independent risk factor for carotid atherosclerosis rather than cerebral small vessel diseases. On the other hand, it is also related to the fact that blood lipids (especially lipoids and cholesterols) are main components of cell membranes and neural myelin sheaths. Lower level of cholesterols will increase the permeability of cell membranes, resulting in bad cellular signal transduction and myelinated synthesis.

7 Other factors

In addition to the above-mentioned factors, there are also some studies showing that LA is probably related to lacunar infarction,[4,34] carotid plaque or stenosis,[35–37] lysophosphatidic acid (LPA),[9] fibriongen (FIB),[38] smoking,[39] alcohol drinking[5,40] etc. However, the specific relevance still remains to be verified by clinical and basic researches.

In summary, LA is related to age, blood pressure, gender, hyperhomocysteinemia, diabetes, blood lipid and other factors. On that account, LA is a consequence of various risk factors. However, the intensity and the mechanism of each risk factor are still lack of positive conclusions, and remain to be further explored by large-scale and well-designed clinical and basic researches, which provide a basis and a support to the prevention and treatment of LA.

Conflicts of Interest Disclosure

The authors have no conflicts of interest related to this article.

References

[1] Merino JG, Hachinski V. Leukoaraiosis: reifying rarefaction. Arch Neurol. 2000; 57(7): 925-926. PMid: 10891972. https://doi.org/10.1001/archneur.57.7.925

[2] Grueter BE, Schulz UG. Age-related cerebral white matter disease (leukoaraiosis): a review. Postgrad Med J. 2012; 88: 79-87. PMid: 22184252. https://doi.org/10.1136/

postgradmedj-2011-130307

[3] Peng CY, Xie HG, Li JM. Related Factors of Leukoaraiosis: A Multi-Logistic Regression Analysis. Chinese Journal of Rehabilitation Theory and Practice. 2009; 15(7): 650-651.

[4] Feng M, Zhang YH, Shou GL, et al. Related Factors of Leukoaraiosis in Patients: A Logic Regression Analysis. Chinese Journal of General Practice. 2011; 9(11): 1677.

[5] Meng XJ, Lin Q, Tian Y, et al. The Case-control Study on Influence Factors of Leukoaraiosis. Chinese Journal of Arteriosclerosis. 2012; 20(2): 153-156.

[6] Wang HP, Wang CY, Jiang CM, et al. Correlation Research on Leukoaraiosis and Multi-factors. Chinese Journal of Integrative Medicine on Cardio/Cerebrovascular Disease. 2010; 8(9): 1057-1058.

[7] Sijens PE, Oudkerk M, De Leeuw FE, et al. 1H Chemical shift imaging of the human brain at age 60-90 years reveals metabolic differences between women and men. Magn Reson Med. 1999; 42: 24-27. https://doi.org/10.1002/(SICI)1522-2594(199907)42:1<24::AID-MRM5>3.0.CO;2-3

[8] Zhou L, Zhou HY. Initial Analysis of Correlation Factors of Leukoaraiosis. West China Medical Journal. 2009; 24(2): 253-255.

[9] Huang WX, Wang BJ, Liu GR, et al. Study of Relationship between Homocysteine and Lysophosphatidic Acid with Leukoaraiosis. China Journal of Modern Medicine. 2012; 22(13): 48-52.

[10] Ren J, Gao YH, Zhang Y. Influence of Blood Pressure Rhythm in Elderly Patients with Leukoaraiosis. China Journal of Modern Medicine. 2011; 13(6): 54-56.

[11] Guo X, Pantoni L, Simoni M, et a1. Blood pressure components and changes in relation to white matter lesions: a 32-year prospective population study. Hypertension. 2009; 54(1): 57-62. PMid: 19487586. https://doi.org/10.1161/HYPERTENSIONAHA.109.129700

[12] Sierra C, Coca A. White matter lesions and cognitive impairment as silent cerebral disease in hypertension. Scientific World Journal. 2006; 21(6): 494-501. PMid: 16633699. https://doi.org/10.1100/tsw.2006.99

[13] Goldstein IB, Bartzokis G, Guthrie D, et al. Ambulatory blood pressure and the brain: a 5-year follow-up. Arch Gerontol Geriatr. 2005; 40(3): 265-273. https://doi.org/10.1212/01.WNL.0000164712.24389.BB

[14] Robert CB. MRI in Central Nervous System. New York: Raven Press; 1993. 229 p.

[15] Tarvonen-Schroder S, Kurki T, Raiha I, et al. Leukoaraiosis and cause of death: a five year follow up. J Neurol Neurosurg Psychiatry. 1995; 58: 586-589. PMid: 7745408. https://doi.org/10.1136/jnnp.58.5.586

[16] Meng YL, Jin Y, Pan XC, et al. Relationship of HYC with Leukoaraiosis. Prevention and Treatment of Cardio-Cerebral-Vascular Disease. 2010; 10(1): 32-34.

[17] Khan U, Hassan A, Vallance P, et al. Asymmetric dimethylarginine in cerebral small vessel disease. Stroke. 2007; 38: 411-413. PMid: 17204687. https://doi.org/10.1161/01.STR.0000254500.27412.ac

[18] Pavlovic AM, Pekmezovic T, Obrenovic R, et al. Increased total homocysteine level is associated with clinical status and severity of white matter changes in symptomatic patients with subcortical small vessel disease. Clin Neurol Neurosurg. 2011; 113: 711-715. PMid: 21802199. https://doi.org/10.1016/j.clineuro.2011.07.004

[19] Feng C, Bai X, Xu Y, et al. Hyperhomocysteinemia associates with small vessel disease more closely than large vessel disease. Int J Med Sci. 2013; 10: 408-412. PMid: 23471237. https://doi.org/10.7150/ijms.5272

[20] Kloppenborg RP, Nederkoorn PJ, vander Graaf Y, et al. Homocysteine and cerebral small vessel disease in patients with symptomatic atherosclerotic disease. The SMART-MR study. Atherosclerosis. 2011; 216: 461-466. PMid: 21411090. https://doi.org/10.1016/j.atherosclerosis.2011.02.027

[21] Hassan A, Hunt BJ, O'Sullivan M, et al. Markers of endothelial dysfunction in lacunar infarction and ischaemic leukoaraiosis. Brain. 2003; 126(2): 424-432. PMid: 12538408. https://doi.org/10.1093/brain/awg040

[22] Hogervorst E, Ribeiro HM, Molyneux A, et al. Plasma homocysteine levels, cerebrovascular risk factors, and cerebral white matter changes (leukoaraiosis) in patients with Alzheimer disease. Arch Neuro. 2002; 59(5): 787-793. https://doi.org/10.1001/archneur.59.5.787

[23] Quadri P, Fragiacomo C, PezzatiR, et al. Homocysteine, folate, and vitamin B-12 in mild cognitive impairment, Alzheimer disease, and vascular dementia. Am J Clin Nutr. 2004; 80: 114-122. PMid: 15213037.

[24] Turaj W, Iskra T, Pulyk R, et al. Plasma homocysteine concentration in patients with ischaemic stroke caused by large or small vessel disease. Pol Merkur Lekarski. 2009; 26: 121-124.

[25] Gouw AA, Van der Flie WM, Fazekas F, et al. Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period: the Leukoaraiosis and Disability study. Stroke. 2008; 39(5): 1414-1420. PMid: 18323505. https://doi.org/10.1161/STROKEAHA.107.498535

[26] Qi D, Wang CX, Jia Q, et al. Relationship between Glycometabolism Abnormality and Leukoaraiosis. Chinese Journal of Stroke. 2010; 5(4): 281-285.

[27] Park JH, Ryoo S, Kim SJ, et al. Differential risk factors for lacunar stroke depending on the MRI (white and red) subtypes of microangiopathy. PLoS One. 2012; 7: e44865. PMid: 23024771. https://doi.org/10.1371/journal.pone.0044865

[28] Kim BJ, Lee SH, Kang BS, et al. Diabetes increases large artery diseases, but not small artery diseases in the brain. Journal of Neurology. 2008; 225 (8): 1176-1181. PMid: 18537055. https://doi.org/10.1007/s00415-008-0864-0

[29] Huang XM, Liu Q, Tan YQ. Discussion on Risk Factors for Leukoaraiosis. Journal of Epileptology and Electroneurophysiology. 2005; 14(3): 170-171.

[30] Yin Y, Wang Q, Zhang ZH. Relationship between Leukoaraiosis and Blood Lipid Levels. Chinese Journal of Rehabilitation Theory and Practice. 2012; 18(11): 1066-1068.

[31] Zhang AJ, Wang SZ, Wang JH. Risk Factors for Leukoaraiosis: A Logistic Regression Analysis. Chinese Journal of Rehabilitation Theory and Practice. 2012; 18(11): 1069-1070.

[32] Guo HZ. Leukoaraiosis. Journal of Clinical Neurology. 2002; 15(1): 3-4.

[33] Zhang DP, Zhang B, Hu CL, et al. The Relationship between Small Vessel Disease and Carotid Atherosclerosis. Chinese Journal of Arteriosclerosis. 2008; 16(6): 487-491.

[34] Gao TL, Zhang Z. Correlation between the ischemic stroke subtypes and its risk factors and leukoaraiosis. Journal of Clinical Neurology. 2009; 22(3): 187-189.

[35] Gao GD, Mo JW. Relationship between Leukoaraiosis and Carotid Atherosclerotic Plaque. The Journal of Practical Medicine. 2006; 22(17): 2030-2031.

[36] Wang GY, Guo HZ, Qu CQ. Study on changes of hemodynamics and regional cerebral blood flow in patients with leukoaraiosis. Journal of Clinical Neurology. 2004; 17(2): 92-94.

[37] Zhao XH, Zhou Y, Chen J, et al. The research on relativity of different kinds of leukoaraiosis and atherosclerosis plague. Journal of Brain and Nervous Diseases. 2010; 18(1): 1-5.

[38] Ren YF, Han N, Yu M, et al. Research on related factors of leukoaraiosis. Chinese Journal of Practical Nervous Disease. 2013; 16(5): 18-20.

[39] Van Dijk EJ, Prins ND, Vrooman HA, et al. Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam Scan study. Stroke. 2008; 39: 2712-2719. PMid: 18635849. https://doi.org/10.1161/STROKEAHA.107.513176

[40] Fan XY, Ren Z, Wei JL, et al. Effect of alcohol drinking on blood lipid and its relationship with cerebrovascular diseases. Laboratory Medicine and Clinic. 2010; 7(14): 1503-1504.