Leukoaraiosis and Stroke

Zhengrong Wu, Bo Song, Yuan Gao, Hui Fang, Yuming Xu*

Department of Neurology, the First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China
E-mail: xuyuming@ZZU.edu.cn, 13903711125@126.com

Abstract: Leukoaraiosis is a common finding in stroke patients, and has been strongly associated with poor outcome of stroke. It showed hypodense on CT scans or hyperintense on T2-weighted MRI on periventricular or subcortical areas (semi-oval center). This article reviews the pathology, pathogenesis, clinical significance and treatment of leukoaraiosis.

[Zhengrong Wu, Bo Song, Yuan Gao, Hui Fang, Yuming Xu. **Leukoaraiosis and Stroke.** *Life Sci J* 2014; 11(6): 383-387]. (ISSN: 1097-8135). http://www.lifesciencesite.com 54

Key words: leukoaraiosis; stroke

The term 'leukoaraiosis' was introduced almost exactly 20 years ago by Vladimir Hachinski and his colleagues.[1] Potter and Merskey to designate bilateral and symmetrical areas in periventricular and centrum semiovale white matter that appeared hypodense on CT scans and hyperintense on T2-weighted MRI. With the rapid rise of MRI brain imaging, a new term was needed for it was becoming clear that diffuse hyperintense on T2-weighted MRI in cerebral white matter were often seen in the context of dementia and vascular risk factors.

Leukoaraiosis often seen in the normal elderly and in association with vascular risk factors such as cognitive impairment, hypertension, diabetes[2]. The name leukoaraiosis were used in this editorial to designate these white matter lesions, as opposed to others related to demyelinating, infectious, toxic, or metabolic processes.[3] Although scientific and technological advancements have made people pay more care to stroke patients in general, it appears as though management of leukoaraiosis remains a perpetual therapeutic problem in vascular neurology. It still remains a remedial destitute in the progressively achieving world of stroke therapeutics. This article reviews the pathology, pathogenesis, clinical significance of stroke and treatment of leukoaraiosis, in the aim of fully realizing the harm of small vessel disease, and controlling the risk, early detection and treatment of risk factors for cerebrovascular. [4]

Pathology

The major pathological findings of leukoaraiosis were myelin pallor gliosis, enlargement of perivascular spaces, and axonal loss.[5,6] It was originally suggested that the selective demyelination which was deemed to a result of 'incomplete' ischaemia might occur. But a single electron microscopy study showed that pallor was almost due to loss of complete nerve fibres.[7] Although the pathology of hyperintensities was much more diverse, a very similar pathology picture was observed in regions of true leukoaraiosis in asymptomatic older adults. The pathological heterogeneity were diminished by Fazekas et al demonstrated that, the lesion severity increases from small punctate hyperintensities to early confluent and then confluent lesions, which almost always had an ischaemic appearance with gliosis, myelin loss and microinfarction.[8] In contrast, periventricular 'caps' and a smooth halo around the lateral ventricles had a non-ischaemic appearance with subependymal gliosis and discontinuity of the ependymal lining.[9] The white matter of the cerebral hemispheres was largely supplied by long, and arterioles that arise from branches of the major cerebral arteries on the pial surface of the brain. The alterations of leukoaraiosis in the structure of these vessels were an invariable feature. In the classical early series changes in the vessels seemed to span a hierarchy of severity from: hyaline thickening and arteriosclerosis (which are regarded as simple small vessel disease) to 'lipohyalinosis'-a term which effects to a more disorganised vessel wall with foamy macrophages, to fibrinoid necrosis.[10] There were more and more last pathology data, but the vascular pathology may have changed. Fibrinoid necrosis were found early phase, possibly it reflected that hypertension were controlled better.[11] However, the early pathology studies, showed by Brun and Englund, that leukoaraiosis was associated with non-amyloid 'fibrohyaline' thickening of arterial walls, as it is in ageing and cerebrovascular disease.[12]

Pathogenesis

The precise pathogenesis linking the pathology of the vessel walls with tissue injury have been the source of considerable controversy. There are some points following about the pathogenesis.

1. Cerebral blood flow decreases

It has been demonstrated in a range of studies and with a wide variety of the Imageological Technique that reduced white matter cerebral blood flow in the context of leukoaraiosis. The studies of brain perfusion

could be useful in this regard. Computed tomographic perfusion derived subcortical white matter cerebral blood flow had been shown to be independently associated with white matter disease severity. [13]

2. Blood-brain barrier dysfunction.

The blood-brain barrier disruption which is a non-ischaemic theory leads to white matter damage, presumably through toxic effects of serum proteins.[14] In patients with leukoaraiosis, exosmotic proteins that were usually confined to the plasma, such as IgG, complement and fibrinogen had been identified in white matter.[15] Similarly, there was a founding that the serum albumin ratio of cerebrospinal fluid in patients with ‘‘vascular dementia’’, which correlated with the degree of leukoaraiosis. We can speculate that the damaged white matter may be the site of blood-brain barrier leakage.[16] Recently, the MRI studies of research organization contrast uptake had demonstrated reduced blood-brain barrier integrity, which was associated with the severity of the visible matter lesions.[17]

3. The endothelium dysfunction

Emerging evidence of endothelial dysfunction in leukoaraiosis provides a unify framework to these theories. Changes in haemodynamics and blood flow, and blood-brain barrier function, may both be part of a broader failure of endothelial function.[18] The research of circulating endothelial markers were beginning to show that a specific pattern of endothelial function which is associated with leukoaraiosis. A recent study[19] showed that patients with a wide range of leukoaraiosis, or multiple small vascular pathological changes in brain magnetic resonance imaging (MRI), had a high level of serum tPA and the low level of fibrinolytic enzyme activators inhibitor type 1 (PAI 1) compared to patients with a solitary leukoaraiosis. The authors speculated that differences in active components of the fibrinolytic system might be involved in the pathophysiology of leukoaraiosis. There was also evidence[18] that suggested chronic endothelial dysfunction assessed by measuring circulating levels of tissue factor (TF), thrombomodulin (TM), intercellular adhesion molecule 1 (ICAM-1), and tissue factor pathway inhibitor (TFPI). Another study showed that[20], after adjustment for potential confounders, ICAM-1 >208 pg/mL and serum tumor necrosis factor-alpha (TNFalpha) >14 pg/mL were independently associated with early neurological deterioration and poor prognosis of patients with leukoaraiosis at 3 months. Moreover, mononuclear cell count may be a risk marker of inflammation. A recent study determined that in patients with more than one small vessel lesion or extensive white matter disease on brain MRI, had higher levels of serum tPA and lower levels of plasminogen activator inhibitor type 1 (PAI-1) compared to patients with a solitary leukoaraiosis. [19]

4. Gene

Leukoaraiosis which is genetic disorders or a group of disorders, may be a characteristics with different phenotypic variable penetrance or expressive, and severity. A number of different genes may be involved in the pathophysiology of leukoaraiosis.[4]

Clinical characteristics

1. Leukoaraiosis and lacunar infarction

Leukoaraiosis and lacunar were common types of small vessel disease. They can occur independently. These two imaging types have recently been shown to differ in their risk factor. Age, hypertension and homocysteine were most strongly associated with ischaemic leukoaraiosis. However, hypercholesterolaemia, diabetes mellitus and myocardial infarction were more associated with lacunar infarction. [21]

Lacunar infarctions were often associated with Leukoaraiosis on MRI. When presented, leukoaraiosis indicated an increased severity of small vessel vascular disease, which may also affect cognitive abilities. Additionally, some studies have found that the degree of cognitive impairment in patients with lacunar infarction were correlation with the severity of leukoaraiosis. And in an interesting study, Leukoaraiosis was common in all the types of ischemic infarction patients. But its development and progression were associated with higher occurrence of strokes mainly in the lacunar type.[22]

2. Leukoaraiosis and transient symptoms with infarction (TSI)

Approximately a third of traditionally defined TIA present with imaging evidence consistent with acute infarction, which is called TSI. TSI - related infarction which were completely very small is one of the most characteristic features.[23] Patients with TSI were more likely to have isolated cortical infarcts and subcortical white matter. The probability of ischemic stroke increased with leukoaraiosis volume increased significantly. And the probability of TSI and ischemic stroke were almost the same, when patients were no leukoaraiosis. Likewise, the regression model implied after excluding patients with chronic white matter infarcts demonstrated that leukoaraiosis volume still remained an independent predictor of clinical status. [24]The median normalized leukoaraiosis volume was roughly speaking 3 times higher in patients with ischemic stroke than TSI. The association between ischemic stroke and increasing leukoaraiosis volume may suggest that leukoaraiosis damage spare capacity in the brain, so that the small infarction can easily overcome threshold, which led to lasting ischemic stroke symptoms[24]. So we could speculate that leukoaraiosis was smaller in TSI compared to ischemic stroke, which partially explain why some patients

develop TSI but others develop ischemic stroke after brain infarction.

3. Leukoaraiosis and ischemic stroke

Leukoaraiosis was more common and severe in patients with ischemic stroke compared to healthy persons, Not only infarct size and location, but also the extent of leukoaraiosis, which together explain the variability in functional outcome in patients with ischemic stroke. Pathology findings in leukoaraiosis includeaxonal changed ranging from mild demyelination to severe axonal damage[25]. The severity of these pathologic changes were related to the severity of leukoaraiosis on MRI.[8] Published studies have shown that using diffusion tensor imaging, MRI, and suggestsed that recruitment and trans cranial magnetic stimulation reorganization of ipsilesional and contralesional brain regions during poststroke recovery need the presence of intact connections between different parts of the brain[26-28]. There were more evidences to support this concept, leukoaraiosis lead to poor outcome after ischemic stroke. Data from the Framingham Heart Study has recently been used to show that there is serious leukoaraiosis baseline to turn over more than one times, the risk of stroke in the future. Moreover, the patients with severe leukoaraiosis had almost four times the the risk of subsequent dementia and in the future more than twice the rate of all-cause mortality. The Greater Cincinnati Stroke in a population-based study, ischemic stroke in patients with severe leukoaraiosis had 90 days of the modified Rankin scale (mRS) that was on average 0.47 points, higher than patients without leukoaraiosis. [29] Similarly, a single center study from Massachusetts General Hospital showed that he average mRS score six months after stroke was 0.8 higher in ischemic stroke patients in the highest quartile of leukoaraiosis compared to the lowest quartile, and that leukoaraiosis was an independent predictor of the odds of a higher mRS after adjustment for potential confounders factors. [24] Again, these important validation data and risk assessment, as other large populationbased studies, including consistent Cardiovascular Health Study, [30] and the Rotterdam Scan Study[31] and demonstrate the clinical relevance of leukoaraiosis.

The last study implied the view that the brain is more susceptible to develop symptomatic stroke in an event of recurrent infarction when leukoaraiosis widely exist. Moreover, this finding may reveal the mechanism of increased stroke risk in individuals with leukoaraiosis, it found that leukoaraiosis impaired capacity to compensate for injury results in occurrence of symptomatic of acute cerebral stroke events. This view was further supported by evidence of leukoaraiosis lead to increased risk of perioperative stroke symptoms after application, were known about the problem of high rate of large cerebral embolism such as carotid artery stenting, carotid endarterectomy,[32] intraoperative shunt placement during carotid endarterectomy,[33] and total aortic arch replacement[34]. Patients with large artery atherosclerosis or acute arterial dissection had high risk for asymptomatic recurrence, but when leukoaraiosis existed extensively, it had 2 to 3 higher odds of symptomatic recurrence. Leukoaraiosis information can also be used to generate the prediction algorithms (along with other independent predictors of clinical outcome) to optimize and minimize the risk benefit from dissolving thrombus treatment..In contrast, in patients with extensive leukoaraiosis, the high risk of intracranial bleeding might outweigh the benefit by thrombolysis.[35]

However, one intriguing finding in the present study was that periventricular WMHs (PVWMHs) and subcortical WMHs (SWMHs) had different effects on ischemic stroke outcome. In terms of location, PVWMHs but not SWMHs were related to predict poor outcome and recurrence of ischemic stroke[29].Why PVWMHs and SWMHs had a different relationship with stroke outcome is unclear. Nonetheless, several theories may explain the difference. SWMHs strikingly disrupted the short association fibers which link adjacent gyri, but PVWMHs affected the long association fibers which connect the more distant cortical areas.[36] therefore, white matter lesions in different location may damage different neural network which would affect the plastic in the process of nerve repair after stroke [37]. Furthermore, PVWMHs were related to diminished cerebral vasomotor reactivity and subsequent cerebral hypoperfusion[38]. However, SWMHs were usually associated with microangiopathy[8].In summary, those suggested that PVWMHs but not SWMHs, in cerebral MRI had impacted on functional recovery after ischemic stroke, regardless of the initial stroke severity and other cardiovascular risk factors.

Treatment

In acute stroke or TIA, there is no evidence to suggest that a different approach to therapy should be taken in the presence of leukoaraiosis. But so far, no one clinical trials or a guide have completed is for prevention and treatment of leukoaraiosis. The most efficient treatment with regard to prevention of leukoaraiosis was still at its minimum. Therefore, in clinical practice, we should follow the the basic principles of the guidelines of cerebrovascular disease which was controlling the risk factors of cerebrovascular disease, such as using the antithrombotic, anticoagulation, statins, antihypertensive, hypoglycemic drugs.[4]

Conclusions

The concept of leukoaraiosis has now been

with us for two decades and has generated controversy, debate and fruitful investigation. The future of leukoaraiosis is contingent upon two main aspects: accurate prognostication and effective management.

Sources of Funding

This study was funded by the Science and Technology Agency of Henan Province (5110400200) and the Natural Science Foundation of Henan Province (0611044800).

Corresponding Author:

Yuming Xu, Department of Neurology, the First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China
E-mail: xuyuming@ZZU.edu.cn, 13903711125@126.com

References

[1] Hachinski, V.C., P. Potter, and H. Merskey, Leuko-araiosis. Archives of Neurology, 1987. 44(1): p. 21.
[2] O'Sullivan, M., Leukoaraiosis. Practical neurology, 2008. 8(1): p. 26-38.
[3] Wiszniewska, M., et al., What is the significance of leukoaraiosis in patients with acute ischemic stroke? Archives of neurology, 2000. 57(7): p. 967-973.
[4] Behrouz, R., A.R. Malek, and M.T. Torbey, Small vessel cerebrovascular disease: the past, present, and future. Stroke research and treatment, 2012. 2012.
[5] Caplan, L.R. and W.C. Schoene, Clinical features of subcortical arteriosclerotic encephalopathy (Binswanger disease). Neurology, 1978. 28(12): p. 1206-1206.
[6] Babikian, V. and A. Ropper, Binswanger's disease: a review. Stroke, 1987. 18(1): p. 2-12.
[7] Yamanouchi, H., S. Sugiura, and M. Tomonaga, Decrease in nerve fibres in cerebral white matter in progressive subcortical vascular encephalopathy of Binswanger type. Journal of neurology, 1989. 236(7): p. 382-387.
[8] Fazekas, F., et al., Pathologic correlates of incidental MRI white matter signal hyperintensities. Neurology, 1993. 43(9): p. 1683-1683.
[9] Schmidt, R., et al., Neuropsychologic correlates of MRI white matter hyperintensities A study of 150 normal volunteers. Neurology, 1993. 43(12): p. 2490-2490.
[10] Lammie, G.A., Pathology of small vessel stroke. British medical bulletin, 2000. 56(2): p. 296-306.
[11] Lammie, G.A., et al., Nonhypertensive cerebral small-vessel disease an autopsy study. Stroke, 1997. 28(11): p. 2222-2229.
[12] Brun, A. and E. Englund, A white matter disorder in dementia of the Alzheimer type: a pathoanatomical study. Annals of neurology, 1986. 19(3): p. 253-262.
[13] Huynh, T., et al., CT perfusion quantification of small-vessel ischemic severity. American Journal of Neuroradiology, 2008. 29(10): p. 1831-1836.
[14] Wardlaw, J., et al., Is breakdown of the blood-brain barrier responsible for lacunar stroke, leukoaraiosis, and dementia? Stroke, 2003. 34(3): p. 806-812.
[15] Akiguchi, I., et al., Blood-brain barrier dysfunction in Binswanger's disease; an immunohistochemical study. Acta neuropathologica, 1997. 95(1): p. 78-84.
[16] Wallin, A., et al., Symptoms, vascular risk factors and blood-brain barrier function in relation to CT white-matter changes in dementia. European neurology, 2000. 44(4): p. 229-235.
[17] Starr, J., et al., Increased blood–brain barrier permeability in type II diabetes demonstrated by gadolinium magnetic resonance imaging. Journal of Neurology, Neurosurgery & Psychiatry, 2003. 74(1): p. 70-76.
[18] Hassan, A., et al., Markers of endothelial dysfunction in lacunar infarction and ischaemic leukoaraiosis. Brain, 2003. 126(2): p. 424-432.
[19] Knottnerus, I.L., et al., Endothelial activation in lacunar stroke subtypes. Stroke, 2010. 41(8): p. 1617-1622.
[20] CASTELLANOS, M., et al., Inflammation -mediated damage in progressing lacunar infarctions: A potential therapeutic target. Stroke, 2002. 33(4): p. 982-987.
[21] Khan, U., et al., Risk factor profile of cerebral small vessel disease and its subtypes. Journal of Neurology, Neurosurgery & Psychiatry, 2007. 78(7): p. 702-706.
[22] Streifler, J.Y., et al., Development and progression of leukoaraiosis in patients with brain ischemia and carotid artery disease. Stroke, 2003. 34(8): p. 1913-1916.
[23] Ay, H., et al., Transient ischemic attack with infarction: a unique syndrome? Annals of neurology, 2005. 57(5): p. 679-686.
[24] Arsava, E., et al., Severity of leukoaraiosis correlates with clinical outcome after ischemic stroke. Neurology, 2009. 72(16): p. 1403-1410.
[25] Fazekas, F., R. Schmidt, and P. Scheltens, Pathophysiologic mechanisms in the development of age-related white matter changes of the brain. Dementia and geriatric cognitive disorders, 1998. 9(Suppl. 1): p. 2-5.
[26] Ward, N., et al., Neural correlates of motor recovery after stroke: a longitudinal fMRI study. Brain, 2003. 126(11): p. 2476-2496.

[27] Ward, N.S., et al., Motor system activation after subcortical stroke depends on corticospinal system integrity. Brain, 2006. 129(3): p. 809-819.
[28] Schaechter, J.D., et al., Microstructural status of ipsilesional and contralesional corticospinal tract correlates with motor skill in chronic stroke patients. Human brain mapping, 2009. 30(11): p. 3461-3474.
[29] Kissela, B., et al., Clinical Prediction of Functional Outcome After Ischemic Stroke The Surprising Importance of Periventricular White Matter Disease and Race. Stroke, 2009. 40(2): p. 530-536.
[30] Longstreth, W., et al., Incidence, Manifestations, and Predictors of Worsening White Matter on Serial Cranial Magnetic Resonance Imaging in the Elderly The Cardiovascular Health Study. Stroke, 2005. 36(1): p. 56-61.
[31] Vermeer, S., et al., Silent brain infarcts and the risk of dementia and cognitive decline. The New England journal of medicine, 2003. 348(13): p. 1215.
[32] Ederle, J., et al., Leukoariosis and perioperative risk of stroke in patients treated for symptomatic carotid stenosis randomised in the International Carotid Stenting Study (ICSS). Cerebrovasc Dis, 2009. 27(suppl 6): p. 10.
[33] Arshad, A., et al., Leukoaraiosis predicts the need for intraoperative shunt placement during carotid endarterectomy. Perspectives in vascular surgery and endovascular therapy, 2009. 21(3): p. 173-177.
[34] Morimoto, N., et al., Leukoaraiosis and hippocampal atrophy predict neurologic outcome in patients who undergo total aortic arch replacement. The Annals of thoracic surgery, 2009. 88(2): p. 476-481.
[35] Neumann-Haefelin, T., et al., Leukoaraiosis is a risk factor for symptomatic intracerebral hemorrhage after thrombolysis for acute stroke. Stroke, 2006. 37(10): p. 2463-2466.
[36] Brodal, P., The central nervous system: structure and function. 2004: Oxford University Press.
[37] Chollet, F., et al., The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. Annals of neurology, 1991. 29(1): p. 63-71.
[38] Gerdes, V.E., et al., Cerebral white matter lesions predict both ischemic strokes and myocardial infarctions in patients with established atherosclerotic disease. Atherosclerosis, 2006. 186(1): p. 166-172.

4/12/2014