New insights into single subcortical infarction

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Abstract: Single subcortical infarction refers to the single infarction occurred in the territory of perforating arteries whose diameter is less than 20mm. SSI has been traditionally called "lacunar infarction" usually considered to be caused by small artery disease that pathologically characterized by lipohyalinosis or fibrinoid degeneration. It accounts for a quarter of all ischemic strokes and was long been considered to have a favorable outcome. However, it's reported that single subcortical infarction can be caused by atherosclerosis in the parental artery through blocking the orifice of branch artery. With the development of image technology, from concept to pathogenesis and then clinical diagnosis and treatment have changed the traditional of the past. The article reviews the definition, etiology and pathogenesis, clinical and imaging features, treatment and other aspects of single subcortical infarction from the new insights.

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1. The definition of SSI

Single subcortical infarction (SSI) which has been traditionally called "lacunar infarction" that may be defined as ischemic infarcts of restricted size in the deeper parts of the brain. Absent from the cerebral and cerebellar cortex, they were best known in the chronic healed stage when they form irregular cavities, 0.5 to 15 mm in diameter, principally in the basal ganglia and basis pontis, and its definition first came from the description of the pathology[1].But now the definition of its diameter has been found may not be perfect.

Jong S.Kim raised the question "Is 15 mm size criterion for lacunar infarction still valid?" first. They conducted a study on strictly subcortical middle cerebral artery (MCA) territory infarction using diffusion-weighted magnetic resonance imaging (DWI). Then they found that since small (diameter <15 mm) subcortical infarcts could be produced by MCA disease or cardioembolism, while a larger infarct could occur without evidence of them, the 'lacunar infarction' has been challenged. The study showed that the infarct diameter in MCA disease was not larger than in SAD ($p = 0.35$), suggested that there seems to be no rationale for the 15 mm size criterion for lacunar or small artery infarction [2]. Another study based on magnetic resonance imaging (MRI) which large subcortical infarcts were diagnosed with a diameter between 15 and 40 mm, while Small deep infarcts were defined with a diameter of less than 15 mm suggested that Clinical features, risk factor profiles, and stroke recurrence rate in patients with a large subcortical infarct only differ slightly from those in patients with small deep or cortical infarcts [3]. Now more and more research defined SSI as the single infarction occurred in the territory of perforating arteries which diameter less than 20mm [4, 5].

A recent study based on high-resolution magnetic resonance imaging (HR-MRI) found that larger SSIs were more closely associated with diabetes mellitus and severe neurological dysfunction but not with the presence of middle cerebral artery plaque, and suggested SSI diameter seems to be associated with anatomic branching variation rather than the mechanism of stroke [6]. Another resent study suggested that based on MRI infarct dimensions and a microangiographic template, it may be possible to estimate the branching order of the artery involved in subcortical infarction. Further, the small data set suggested that reliance on an axial dimension of 15-20 mm may not be the best approach to classifying subcortical infarction [7].

The definition of the diameter of SSI needs to be confirmed in a larger data set in the further research.

2.The etiology and pathogenesis of SSI

SSI has been traditionally called "lacunar infarction" usually considered to be caused by small artery disease (SAD) that pathologically characterized by lipohyalinosis or fibrinoid degeneration [8]. And in the past it was considered to be caused by SAD associated with high blood pressure, smoking and diabetes, atherosclerosis was not considered one of the causes. It is rarely carried out further research on the artery.

In the 1970s, Fisher reported three autopsy cases of paramedian pontine infarctions caused by the occlusion of perforating branches of the basilar artery

(BA) [9]. Later, LouiR etc. raises deep perforators mainly include three aspects: plaque from the parental artery blocking a branch artery; plaque of the parental artery extending into the branch artery, and plaque of branch artery orifice itself. Micro dissection, plaque bleeding and blood platelet fibrin plugs in branch artery stenosis or occlusion played a leading role [10]. Bogousslavsky etc. analysed 16 cases of perforators artery infarction patients, including them 10 patients with angiographic showed that intracranial artery stenosis occurred in the orifice of deep perforators arterial,and suggsted that perforators artery occlusion may be due to local atherosclerosis blocked the perforators openings, rather than a small artery lesions itself.[11] Huang Jiaxing ect. checked on 30 patients with micro emboli monitoring and DWI, and found 10 SSI patients did not detect emboli, its mechanism may be an atherosclerotic plaque of middle cerebral artery itself blocked the orifice of perforators artery, thus formed the lacunar infarction.[12]

Fisher as early as in 1965, has put forward that the micro switch could lead to lacunar infarction by entering into the perforators' artery occasionally [1]. Later Santamaria et al found that 8 basal ganglia and internal capsule infarction patients had sources of cardiogenic emboli, but had no other source of small artery. This suggested that embolization may be one mechanism of perforating artery infarction [13]. Huang Jiaxing ect. found that thromboembolic off from large artery stenosis could not only lead to shedding cortical artery embolization, but also stay in the deep perforating artery leading to "lacunar-like" infarction, suggesting that embolism may be one of the causes of the small infarction in deep perforating artery territory [12].

These findings suggested that SSI can be caused by a variety of causes. The pathological of the perforating branches showed that perforating branches disease leading to symptomatic infarcts was mainly perforators artery orifice atherosclerosis lesions [9,14,15]. SSI may be multiple etiologies, but a partial view, it can due to focal atherosclerotic plague of the parent artery disease (PAD) blocking the orifice of a branch artery and branch artery itself.

A study in Korea investigated 173 cases of lacunar stroke (clinical lacunar syndrome plus small deep infarction on MRI), according to the MRA or digital subtraction angiography (DSA) examination results, divided the patients into with and without PAD group, and compared 1-year recurrence rate of stroke with the large artery disease, and found that the recurrence rate of the group with PAD was much higher than not accompanied with PAD, but was similar to the large artery disease. Moreover, the recurrent stroke, almost all located in the parent artery distribution, suggesting that there were different causes and mechanisms of lacunar stroke [16].

PAD is a pathologic entity diagnosable with certainty only at postmortem. However, clinical data can at least raise the suspicion that atheromatous branch disease is likely to be responsible for certain clinical syndromes. Recently, With the development of imaging technology, especially the development of HR-MRI and high-field magnetic resonance (7.0 T) provides a more direct radiographic evidence of this discovery. It has been shown that the 7-tesla MRI with ultra-high resolution accurately demonstrates small intracranial perforators [17-20]. A recent study based on ultra-high-field(7.0 T) MRI and a three dimensional image demonstrated that 7.0T MRI together with a three dimensional image analysis and modeling technique could provide information for detection of the vessel related to the infarct. In addition, three dimensional image analysis and modeling of vessels could further provide quantitative information on the microvessel structures comprising diameter, length and tortuosity [21].

Studies have reported that HR-MRI can show the vessel wall structure and, therefore, detect early atherosclerotic changes such as plaques, wall thickening, and arterial remodeling, even in patients with normal findings on MRA [22, 23]. SSI with parental artery disease (SSIPAD) can be found in the parent artery perforators' obvious atherosclerotic lesions and even block.

However, SSIPAD has been neglected in previous stroke sub-type classifications such as Trial of Org 10172 in Acute Stroke Treatment (TOAST), Stop Stroke Study Trial of Org 10172 in Acute Stroke Treatment (SSS-TOAST), and Atherosclerosis-Small vessel diseasecardiac source-other cause (ASCO). And for most studies on stroke subtypes in Chinese, the presence of parental artery disease among patients with SSI had not been investigated. With the development of the research, branch artery disease has been referred to in Chinese Ischemic Stroke Subclassification (CISS).

3.The clinical and imaging features of SSI

Hospital-based studies show that the frequencies of SSI among Chinese stroke patients range from 25% to 30% [24-27]. SSIPAD is one of the main stroke mechanisms in patients with intracranial atherosclerotic stroke (ICAS). It has long been recognized that intracranial large artery disease is more common among Chinese than Caucasians [28].

A study found that short-term stroke recurrence rate of SSIPAD patients was similar with large artery atherosclerosis and apparently higher than SSI associated with SAD [16]. But there is little research in this area, and further studies with more patients and

longer follow-up are needed to clarify whether SSIPAD has influence on outcome.

SSIPAD is an atherosthrombotic disease. A recent study of 335 SSI patients with PAD and 114 with SAD has found that the former had a higher prevalence of atherosclerosis such as asymptomatic cerebral artery atherosclerosis and coronary heart disease, but had a lower prevalence of SAD indicators, such as leukoaraiosis (LA) and microbleeds [4]. Another study reported that SSIPAD was also associated with atherosclerotic lesions in other vascular beds and older age [29]. A MRA based study has found that nonrelevant stenosis was also more prevalent in the PAD than in the SAD group [30].

Kim think that the pathogenesis of linear lesions in SSI may be associated with atherosclerosis, and round or oval shape lesions may be more related to lipid hyaline degeneration or fibrin degradation[31]. A study based on mostly MRA included 86 patients in the proximal SSI (pSSI) group and 123 in the distal SSI (dSSI) group in Chinese people found that the lesion diameter in the pSSI group was significantly greater than that in the dSSI group, and the composition ratins in patients in diabetes mellitus, hyperlipidemia, the parent artery disease, other intracranial arterial stenosis and extracranial artery stenosis were significantly higher than those in the dSSI group. However, the composrion ratios in patients with hypertension and leukoaraiosis were significantly lower than those in the dSSI group. This suggested the clinical characteristics of SSI are different in classification based on the relationship between the lesion sites and MCA. SSI of proximal perforating artery may be caused by the large artery disease, and SSI of the remote areas are mostly caused by small artery disease [5],and a recent study based on HRMRI found that compared with dSSI, pSSI is closely associated with large lesions, severe clinical symptoms, and superiorly located MCA plaques [32].Caplan categorized the causes into three groups: plaque from the parental artery blocking the orifice of a branch artery, plaque of the parental artery extending into the branch artery and obstruction of the proximal portion of branch artery by microatheroma [10].

The lesion volume is generally larger in patients with SSIPAD [33,34]. However, a recent study based on HRMRI found that larger SSIs were more closely associated with diabetes mellitus and severe neurological dysfunction but not with the presence of middle cerebral artery plaque, and suggested SSI diameter seems to be associated with anatomic branching variation rather than the mechanism of stroke [6].

SSI was previously considered to be stable course, low recurrence and low mortality [35-41]. But research indicated the clinical course of about 12% to 36% patients are unstable and tend to occur early neurological deterioration (END), showing the symptoms of neurological defects in the pathogenesis of hours or days continued to increase, and ultimately may lead to severe disability[42-44]. There may exist identification clues from the difference in the image.

The exact mechanisms of END is not clear, hemodynamic factors, thrombosis, excitatory toxic effect, inflammatory reaction and elevated serum homocysteine levels are thought to be the possible mechanism [42,45-47]. It still remains unclear whether SSIPAD is more likely to lead to END. It has produced inconsistent conclusions in patients with SSIs on MCA territory. While some studies reported that SSI with MCA atherosclerosis is more often associated with END or an unstable clinical course [48, 16], others showed END was associated with the sub-acute DWI lesion volume increase but not MCA atherosclerosis [49].

A study based on DWI showed that END was found in 28 (39.44％) patients with linear ISSI and 25 (18.12％) patients with round or oval SSI. Univariate analysis indicated that lesion pattern. sex. initial NIHSS score，coronary heart disease，ipsilateral MCA stenosis and intracranial atherosclerotic stenosis were significantly associated with END. Logistic regression analysis suggested that linear lesion (P=0.019) was an independent predictor of END, and patients with linear SSI were more prone to present fluctuated clinical course which may be helpful in predicting patients with END [50]. In a study of 56 patients with unilateral pontine base infarction that extend to the ventral surface, 22 patients (39%) had PAD and 15 patients (27%) had END, and the PAD was not significantly related to END, but was closely related to the subacute increase in lesion volume [34]. But in another study of lateral thalamic infarction, the atherosclerosis was significantly associated with both adverse functional outcomes and increased sub-acute lesion volume [33]. A recent study based on HRMRI found that albuminuria is associated with END and infarct volume expansion in patients with SSI in the lenticulostriate artery territory [51].

These results suggest, the lesion volume increase and END in SSIPAD patients may be related to greater extension of atherothrombosis. HRMRI can find more potential plaque, and the possibility is greater of proximal level due to the parent artery.

4. The treatment of SSI

It was wrong to equal SSI to SAD before. Even if you don't think the atherosclerotic lesions of perforators artery orifice are the main cause of SSI,

should at least consider wearing both atherosclerotic lesions of perforators artery orifice and lipohyalinosis or fibrinoid degeneration these two kinds of pathological changes.

Sps3 research results support the current guidelines that recommend against the use of the combination of clopidogrel plus aspirin for secondary stroke prevention and now extend this advice to those with recent small subcortical strokes, or lacunar infarcts, that have been confirmed by MRI. Subsequent research found although the reduction in stroke was not significant, the results support that in patients with recent lacunar stroke, the use of a systolic-blood-pressure target of less than 130 mm Hg is likely to be beneficial [52].

Because the SSIPAD has obvious characteristic of large artery atherosclerosis, physicians should be alert for systemic arterial atherosclerosis appearance, and should give fight on atherosclerosis, control blood sugar and adjusting blood fat in the treatment, especially in the Asian populations with a higher frequency of intracranial stenosis. Even if the artery stenosis was detected, but still cannot ignore the potential of atherosclerotic lesions, such as the light degree of artery disease or the proximal part of perforators artery lesions, and due to the limited existing vessel imaging technology, it is difficult to be checked out this part of the lesions or has not been taken seriously.

SSI caused by SAD is more often associated with small vessel disease characteristics, clinici ans should give positive to reduce blood press, but should be careful for double drug combination antiplatelet therapy. Because previous studies have shown that SSI in distal perforators artery area is prone to hemorrhagic transformation, and LA is also likely to increase the risk of cerebral hemorrhage [53-55].

5. Conclusions

In conclusion, we clarified the SSIPAD is an important classification of stroke. We have to realize that SSIPAD is an important reason of SSI, different from SAD. It is one of the most important classifications of atherothrombotic stroke even if it has been classified as SAD erroneously. Further researches are needed to discuss the prevalence of SSIPAD, and to formulate an appropriate stroke classification including SSIPAD. Prevention and treatment trials should consider this important stroke classification in the future.

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References

1. Fisher CM. Lacunes: small, deep cerebral infarcts. Neurology 1965; 15: 774-84.
2. Cho AH, Kang DW, Kwon SU, Kim JS. Is 15 mm size criterion for lacunar infarction still valid? A study on strictly subcortical middle cerebral artery territory infarction using diffusion-weighted MRI. Cerebrovascular diseases. 2007; 23(1): 14-9.
3. Halkes PH, Kappelle LJ, van Gijn J, van Wijk I, Koudstaal PJ, Algra A. Large Subcortical Infarcts: Clinical Features, Risk Factors, and Long-Term Prognosis Compared With Cortical and Small Deep Infarcts. Stroke. 2006; 37: 1828-1832.
4. Hyun-Wook Nah, Dong-Wha Kang, Sun U. Kwon, Jong S. Kim. Diversity of Single Small Subcortical Infarctions According to Infarct Location and Parent Artery Disease: Analysis of Indicators for Small Vessel Disease and Atherosclerosis. Stroke. 2010; 41: 2822-2827.
5. Duan Zuo-Wei，Sun Wen，Huang Zhi-Xin，Cai Qian-kun, Xiao Lu-lu, Chen Xiang-liang，Cao Li-ping，Xiong Yun-yun，Xu Ge lin，Liu Xin-feng. Correlation between since small subcortical infarction and artery stem lesions in niddle cerebral artery territory: a prospective case series study. Int J Cerebrovasc Dis, June 2013, Vol. 21, No. 6: 435-439.
6. Kim BJ, Lee DH, Kang DW, Kwon SU, Kim JS.et al. Branching Patterns Determine the Size of Single Subcortical Infarctions. Stroke. 2014 Mar 20. [Epub ahead of print]
7. Phan TG, van der Voort S, Beare R, Ma H, Clissold B, Holt M, Ly J, Foster E, Thong E, Stuckey S, Cassell MD, Srikanth V. Dimensions of subcortical infarcts associated with first-to third-order branches of the basal ganglia arteries. Cerebrovasc Dis. 2013; 35 (3): 262-7.
8. Fisher CM. Lacunar strokes and infarcts: a review. Neurology. 1982; 32: 871–876.
9. Fisher CM, Caplan LR. Basilar artery branch occlusion: a cause of pontine infarction. Neurology 1971; 21: 900–5.
10. Caplan LR. Intracranial branch atheromatous disease: a neglected, understudied, and

underused concept [J]. Neurology. 1989; 39: 1246-1250.
11. Bogousslavsky J, Regli F, Maeder P. Intracranial large-artery disease and “lacunar” infarction [J]. Cerebrovasc Dis. 1991; 1: 154-159.
12. Wong KS, Gao S, Chan YL, et al. Mechanisms of acute cerebral infarctions in patients with middle cerebral artery stenosis: a diffusion-weighted imaging and microemboli monitoring study [J]. Ann Neurol. 2002; 52: 74-81.
13. Santamaria J, Graus F, Rubio F, et al. Cerebral infarction of the basal ganglia due to embolism from the heart [J]. Stroke. 1983; 14: 911-914.
14. Fisher CM. Bilateral occlusion of basilar artery branches [J]. J Neurol Neurosurg Psychiatry. 1977; 40: 1182-1189.
15. Fisher CM. Capsular infarcts：the underlying vascular lesions [J]. Arch Neurol. 1979; 36：65-73.
16. Bang OY, Joo SY, Lee PH, et a1. The course of patients with lacunar infarcts and a parent arterial lesion: similarities to large artery vs small artery disease [J] . Arch Neurol. 2004; 61: 514-519.
17. Cho ZH, Kang CK, Han JY, et al. Observation of the lenticulostriate arteries in the human brain in vivo using 7.0T MR angiography. Stroke. 2008; 39: 1604-1606.
18. Kang CK, Park CW, Han JY, et al: Imaging and analysis of lenticulostriate arteries using 7.0-tesla magnetic resonance angiography. Magn Reson Med 2009; 61: 136-144.
19. Song HS, Kang CK, Kim JS et al. Assessment of pial branches using 7-tesla MRI in cerebral arterial disease. Cerebrovasc Dis. 2010; 29: 410.
20. Chung JW, Kim BJ, Sohn CH, Yoon BW, Lee SH et al. Branch atheromatous plaque: a major cause of lacunar infarction (high-resolution MRI study). Cerebrovasc Dis Extra. 2012; 2: 36-44.
21. Chang-Ki Kang, Stefan Worz, Wei Liao, Chan-A Park, Young-Bo Kim, Cheol-Wan Park, Young-Bae Lee, Karl Rohr, and Zang-Hee Cho. Three dimensional model-based analysis of the lenticulostriate arteries and identification of the vessels correlated to the infarct area: preliminary results. International Journal of Stroke. Vol 7. October 2012; 558-563.
22. Li ML, Xu WH, Song L, Feng F, You H, Ni J, et al. Atherosclerosis of middle cerebral artery: evaluation with high-resolution MR imaging at 3T. Atherosclerosis. 2009; 204: 447-452.
23. Ma N, Jiang WJ, Lou X, Ma L, Du B, Cai JF, et al. Arterial remodeling of advanced basilar atherosclerosis: a 3-tesla MRI study. Neurology. 2010; 75: 253-258.
24. C.Y. Huang, F.L. Chan, Y.L. Yu, E. Woo, D. Chin. Cerebrovascular disease in Hong Kong in Chinese. Stroke. 21 (1990); pp: 230-235.
25. R. Kay, J. Woo, L. Kreel, H.Y. Wong, R. Teoh, M.G. Nicholls. Stroke subtypes among Chinese living in Hong Kong.Neurology. 42 (1992); pp: 985-987.
26. P.K. Yip, J.S. Jeng, T.K. Lee, Y.C. Chang, Z.S. Huang, S.K. Ng et al. Subtypes of ischemic stroke, a hospital-based stroke registry in Taiwan. Stroke. 28 (1997); pp: 2507-2512.
27. L.E. Davis, J.G. Xie, A.H. Zou, J.Y. Wang, Y.J. Liu, T.X. Go et al. Deep cerebral infarcts in the People's Republic of China. Stroke. 21 (1990); pp: 394-396.
28. E. Feldmann, N. Daeault, E. Kwa, K.J. Ho, M.S. Pessi, P. Langenberg et al. Chinese-white differences in the distribution of occlusive cerebrovascular disease. Neurology. 40 (1990); pp: 1541-1545.
29. Choi HY, Yang JH, Cho HJ, Kim YD, Nam HS, Heo JH. Systemic atherosclerosis in patients with perforating artery territorial infarction.Eur J Neurol. 2010; 17: 788–93.
30. Ryoo S, Park JH, Kim SJ, Kim GM, Chung CS, Lee KH, Kim JS, Bang OY. Branch occlusive disease: clinical and magnetic resonance angiography findings. Neurology. 2012 Mar 20; 78(12): 888-896.
31. Kim JT，Yoon GJ，Park MS，et a1. Lesion patterns of small deep infarcts have difierent clinical and imaging characteristics. Eur Neurol. 2010; 63: 343-349.
32. Yoon Y, Lee DH, Kang DW, Kwon SU, Kim JS.et al. Single subcortical infarction and atherosclerotic plaques in the middle cerebral artery: high-resolution magnetic resonance imaging findings. Stroke. 2013 Sep; 44(9): 2462-7.
33. Kim HJ, Song JM, Kwon SU et al. Right-left propensity and lesion patterns between cardiogenic and aortogenic cerebral embolisms. Stroke. 2011; 42: 2323-5.
34. Kim JS, Cho KH, Kang DW, Kwon SU, Suh DC. Basilar artery atherosclerotic disease is related to subacute lesion volume increase in pontine base infarction. Acta Neurol Scand. 2009; 120: 88–93.
35. Gandolfo C, Moretti C, Dall’Agata D, Primavera A, Brusa G, Loeb C. Long-term prognosis of patients with lacunar syndromes. Acta Neurol Scand. 1986; 74: 224-229.
36. Bamford J, Sandercock P, Jones L, Warlow C. The natural history of lacunar infarction: the Oxfordshire Community Stroke Project. Stroke. 1987; 18:545-551.

37. Sacco SE, Whisnant JP, Broderick JP, Philips SJ, O'Fallon WM. Epidemiological characteristics of lacunar infarcts in a population. Stroke. 1991; 22: 1236-1241.
38. Miyao A, Teramoto J, Takahashi A. Leukoaraiosis in relation to prognosis for patients with lacunar infarction. Stroke. 1992; 23: 1434-1438.
39. Boiten J, Lodder J. Prognostic for survival, handicap and recurrence of stroke in lacunar and superficial infarction. Cerebrovasc Dis. 1993; 3: 221-226.
40. Clavier I, Hommel M, Besson G, Noelle B, Perret F. Long-term prognosis of symptomatic lacunar infarcts: a hospital-based study. Stroke. 1994; 25: 2005-2009.
41. Salgado AV, Ferro JM, Gouveia-Oliveira A. Long-term prognosis of first-ever lacunar strokes: a hospital-based study. Stroke. 1996; 27:661-666.
42. Del Bene A, Palumbo V, Lamassa M，et a1. Progressive lacunar stroke: review of mechanisms，prognostic features，and putative treatments．Int J Stroke. 2012; 7: 321-329.
43. Yamamoto Y, Ohara T, Hamanaka M, Hosomi A, Tamura A, Akiguchi I. Characteristics of intracranial branch atheromatous disease and its association with progressive motor deficits. J Neurol Sci. 2011; 304: 78-82.
44. Steinke W, Ley SC. Lacunar stroke is the major cause of progressive motor deficits. Stroke 2002; 33:1510-6.
45. Chen Ke-nan，Guo Shun-yuan ，Chen Gui-hua，Geng Yu. Progressive motor deficit caused by isolated unilateral pontine infarction extending to the pontine surface. Chin J Neurol. March 2013; 46: 172-175.
46. Alawneh JA, Moustafa RR, Baron JC. Hemodynamic factors and perfusion abnormalities in early neurological deterioration．Stroke. 2009; 40: 443-450.
47. Kwon HM, Lee YS, Bae HJ, Kang DW.Homocysteine as a predictor of early neurological deterioration in acute ischemic stroke. Stroke. 2014 Mar; 45 (3): 871-3.
48. Adachi T, Kobayashi S, Yamaguchi S, Okada K. MRI findings of small subcortical 'lacunar-like' infarction resulting from large vessel disease.J Neurol. 2000; 247: 280-5.
49. Cho KH, Kang DW, Kwon SU, Kim JS. Lesion volume increase is related to neurologic progression in patients with subcortical infarction. J Neurol Sci. 2009; 284: 163-7.
50. Duan Zuo-Wei, Sun Wen, Huang Zhi-Xin, Cai Qian-kun, Li Hua, Xiao Lu-lu, Cao Li-ping, Chen Xiang-liang, Xiong Yun-yun, Xu Ge-lin, Liu Xin-feng. Relationship between lesion patterns of isolated small subcortical infarction and early neurological deterioration. Chin J Neurol, November 2013; Vol. 46, No, 11: 735-738.
51. Umemura T, Senda J, Fukami Y, Mashita S, Kawamura T, Sakakibara T, Sobue G. Impact of albuminuria on early neurological deterioration and lesion volume expansion in lenticulostriate small infarcts. Stroke. 2014 Feb; 45 (2): 587-90.
52. SPS3 Study Group, Benavente OR, Coffey CS, Conwit R, Hart RG, McClure LA, Pearce LA, Pergola PE, Szychowski JM. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. Lancet. 2013 Aug 10; 382 (9891): 507-15.
53. Aguilar MI ， Freeman WD. Spontaneous intracerebral hemorrhage. Semin Neurol. 2010; 30: 555-564.
54. Caprio FZ，Maas MB，Rosenberg NF，et a1. Leukoaraiosis on magnetic resonance imaging correlates with worse outcomes after spontaneous intracerebral hemorrhage. Stroke. 2013; 44: 642-646.
55. Folsom AR, Yatsuya H, Mosley TH Jr, et a1. Risk of intraparenchymal hemorrhage with magnetic resonance imaging-defined leukoaraiosis and brain infarcts. Ann Neurol. 2012; 71: 552-559.

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