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Overview-Research Progress of Leukoaraiosis

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Abstract

In 1987, Hachinski *et al.* [1] proposed Leukoaraiosis (LA) as an imaging academic term. Since then, LA and other cerebrovascular diseases have become the research focus of scholars at home and abroad. However, the molecular, cellular and pathogenesis of cerebrovascular disease are still unclear. Cerebral small vessel disease is caused by the lesions of perforating arteries, capillaries and veins of the brain. Modern imaging technology makes it possible to classify these diseases that can not be directly distinguished in clinical practice. The imaging features of cerebral infarction include cerebral microvascular atrophy. At present, a large number of studies have been carried out around LA, such as the pathogenesis, risk factors, imaging manifestations and classification, pathophysiological changes, hemodynamics, gene polymorphism and so on. In addition, although LA belongs to the category of cerebral small vessel disease, more scholars believe that there are countless links between large artery atherosclerosis and LA, and to some extent, have the same pathogenesis. This paper reviews the following aspects.

Keywords

Leukoaraiosis (LA), Cerebral Small Vessel Disease, Large Artery Atherosclerosis

1. Imaging and Clinical Manifestations of LA

As an imaging academic language, LA has multiple pathological changes [2]. The pathological signs are myelination [3] and axon loss, patchy demyelination, and ependymal erosion in white matter lesions [4]. In the T2 sequence and Fluid Attenuated Inversion Recovery (FLAIR), LA is characterized by a high white matter signal. Therefore, LA is equivalent to "white matter hyperintensity" and "white matter lesion" in the literature. According to the imaging features, LA can be divided into periventricular type and subcortical type. According to the anatomical characteristics, the deep periventricular white matter mainly originates from the choroidal

artery of the subependymal artery or the terminal branch of the striatal artery, which results in the "distal blood supply area" of the white matter area within 3 - 10 mm around the ventricular wall, that is, the watershed area of arterial blood supply [5] [6]. However, subcortical white matter mainly originated from the long perforating arteries of the pia mater artery, which were long and curved. Therefore, during cerebral ischemia or hypoperfusion, these regions are prone to ischemic changes, resulting in corresponding imaging changes [7]. However, if there are various risk factors of cerebrovascular disease, cerebral arteriosclerosis will gradually occur, resulting in clinical manifestations [8], such as dyskinesia, gait abnormalities, urinary incontinence [9], cognitive dysfunction [10]-[15], depression, especially memory impairment. Moreover, patients with LA are prone to lacunar infarction, which is easy to cause long-term recurrence of stroke [16], and aggravate the subcortical cognitive impairment in TIA or minor stroke [15]. A clinical study conducted by Ryu [17] showed that the volume of LA is related to the clinical outcome of stroke.

Cerebral atrophy is a new emerging feature of cerebral small vessel disease, and this atrophy of the gray matter is usually progressive and documented mainly in patients with stroke of the lacunar type (see and comment on the study published in M.; Arboix [18].

The evaluation criteria of LA: Fazekas method was used to score LA lesions in paraventricular and deep subcortical white matter [19].

The score of paraventricular lesions was as follows:

0: no lesions;

1 point: LA was in the shape of a cap or pencil;

2 points: LA showed a smooth halo shape;

3 points: LA was irregular in shape and extended to deep white matter.

The score of deep white matter lesion was as follows:

0: no lesions;

1 point: LA showed punctate lesions;

2 points: the dot-like LA began to fuse;

3 points: large area fusion of LA.

2. Risk Factors for LA

Vascular risk factors for LA include age, hypertension [20] [21], diabetes [22] [23], smoking [24], fibrinogen [25], hyperuricemia [26], etc. These factors increase the prevalence of LA. There are also unidentified risk factors such as gender [27] [28], hyperlipidemia [24] [29] [30], hyperhomocysteinemia [22] [31], asymmetric dimethylarginine [20], carotid atherosclerosis [32] and so on. Among them, Etherton *et al.* [28] found that women have worse outcomes after acute ischemic stroke than men, which proves that the integrity of white matter is related to gender. Guan *et al.* [20] proposed that age, hypertension and asymmetric dimethylarginine are risk factors for LA. Asymmetric dimethylarginine may be related to uric acid and serum creatinine; it is produced by endothelial cells [33] and is an endogenous nitric oxide synthase inhibitor; it competitively inhibits L-arginine and

the combination of nitric oxide leads to reduced nitric oxide bioavailability and vascular endothelial damage. Based on the population-based 3C-Dojon Study and the French Epidemiology of Vascular Aging Study, the results showed that increased serum triglyceride levels were related to the increase in the volume of LA, while the level of low-density lipoproteins was negatively correlated with LA [29]. In the Cardiovascular Health Study, LDL and LA are also negatively correlated [34]. Shi *et al.* [23] have provided clinicians with an auxiliary tool to predict and diagnose LA, such as age, hypertension, diabetes, hypertriglyceridemia, etc. and found lacunar infarction. Medical history and history of cerebral hemorrhage are related to LA. If the risk factors of cerebrovascular disease exist in the middle-aged population, the performance is especially important, but the importance of various risk factors in different age groups is different. A large multicenter study in South Korea included 11 stroke centers and 2699 first-onset stroke patients. The results showed that age, hypertension, atrial fibrillation, and left ventricular hypertrophy were independently associated with white matter lesions [35].

At present, there are many controversies about the risk factors of LA. Although many studies believe that hypertension is closely related to LA, Dickie *et al.* [36] observed the changes of blood pressure in patients with acute ischemic stroke at 5 time points within one week after the onset of acute ischemic stroke, and found that the change of blood pressure was not related to LA, and also had no correlation with adverse clinical outcomes after acute stroke. In addition, Yano *et al.* [37] included 755 middle-aged and elderly community residents in the Genoa study. They found that the increase of nocturnal hypertension in black people reflected the integrity and executive function of white matter in frontal lobe, while there was no significant difference among white people. But so far, it is not clear whether most of the effects of hypertension directly affect the brain, or whether hypertension leads to a series of vascular sclerosis, and then affects the white matter and cognitive function. More longitudinal studies are needed to observe and clarify the series of effects of risk factors on LA.

3. Pathogenesis of LA

The exact pathogenesis of LA is still unclear and controversial [8]. According to the pathological characteristics, the subependymal white matter lesions are considered to be the damage of the ependymal layer, while from the anatomical characteristics; it is believed that the lesions are caused by chronic ischemia. Due to its special anatomical structure, the pathogenesis of LA is different from other common cerebrovascular diseases. Scholars believe that its pathogenesis includes cerebral hypoperfusion, destruction of blood-brain barrier, endothelial injury and oxidative stress, amyloid beta deposition, gene polymorphism, etc.

3.1. Cerebral Hypoperfusion

Because the white matter is located in the watershed of arterial blood supply, it is

sensitive to ischemia and easy to be damaged, resulting in many clinical symptoms. More evidences support that cerebral hypoperfusion is the pathogenesis of La. In recent years, many studies [38] [39] [40] have shown that regional ischemia in the white matter area may be related to hemodynamics, and the most recognized type is the impairment of cerebral autoregulation function and intracranial hypoperfusion. Tsivgoulis *et al.* [41] summarized some literature data and pointed out that in five studies, cerebrovascular hemodynamic changes occurred in patients with vascular dementia, and cerebrovascular reserve function was damaged and exhausted. This study suggests that the correlation between cognitive impairment and vascular risk factors can be evaluated by observing intracranial hemodynamics. Barker *et al.* [42] [43] found that the ratio of myelin associated glycoprotein to proteolipid protein-1 is a powerful marker of hypoperfusion in patients with white matter lesions, which decreases with the aggravation of white matter lesions.

3.2. Blood Brain Barrier Damage

Another pathogenesis of LA is the damage of blood-brain barrier. A meta-analysis summarized 31 related studies. The results showed that the permeability of blood-brain barrier increased with age in normal people. The permeability of blood-brain barrier in patients with progressive symptoms was significantly higher than that in patients with non-progressive symptoms. This result suggests that the damage of blood-brain barrier may be an important pathogenesis of LA [44]. Giwa *et al.* [45] found that the leakage proteins include fibrinogen, immunoglobulin, thrombomodulin, etc. and this leakage can occur in subcortical gray matter and white matter, and also in normal gray matter and white matter, which is related to microglia. Valdes Hernandez *et al.* [46] studied the integrity of Cerebrospinal Fluid (CSF) in patients with LA by magnetic resonance imaging, and found that the tissue structure and cerebrospinal fluid permeability of La patients increased. It was speculated that the blood-brain barrier was damaged, and the damage of tissue structure was homogeneous, and the change of abnormal structure and normal structure was not very obvious. So far, although many studies have shown that the blood-brain barrier permeability of LA patients has changed, it has not been confirmed by longitudinal studies.

3.3. Endothelial Cell Injury and Oxidative Stress

The pathogenesis of cerebrovascular disease may be the dysfunction and activation of endothelial cells, which leads to cerebral hypoperfusion and increased blood-brain barrier permeability, and interaction [47]. Endothelial dysfunction is due to the formation of imbalance oxygen free radicals induced by continuous ischemia, reperfusion injury or inflammation, resulting in oxidative stress reaction, which leads to the formation of peroxynitrite, lipid peroxidation, protein modification, matrix metalloproteinase activation and DNA damage [48]. Markers of endothelial dysfunction include intercellular adhesion molecule-1 and throm-

bomodulin combined with homocysteine [49]. Oxidative stress can cause brain damage and cognitive impairment related to cerebrovascular disease. Reduced Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase is the main active oxygen producing enzyme in cerebral vessels. The drug treatment strategy of NADPH oxidase inhibitors can inhibit oxidative stress response [50].

In the Australian stroke prevention study, a cohort study of community residents found that intercellular adhesion molecule-1 was an independent predictor of La progression [51]. Rotterdam Scan study found that persistent and elevated Hcy levels were associated with static cerebral infarction, and Hcy levels were also associated with increased LA [52]. Framingham offspring study found that the increase of Hcy level in middle-aged people was related to the decrease of brain volume, and to the increase of static cerebral infarction focus, but not to the increase of LA volume [53].

3.4. Inflammatory Biomarkers

Neuroinflammatory lesions play an important role in the occurrence and progression of LA [4]. C-Reactive Protein (CRP) and interleukin-6 (IL-6) are the most common biological inflammatory markers. CRP is a substance that is synthesized in the liver and reacts with IL-6 in acute phase. One part of IL-6 stimulates the immune response and is secreted by T cells and macrophages; the other part is inflammatory chemokines secreted by vascular smooth muscle cells. IL-6 is associated with myocardial infarction, stroke, cardiovascular death and peripheral artery disease [54].

Some studies have found that the increased levels of IL-6 and CRP are associated with LA and static cerebral infarction [55]. In the Rotterdam Scan Study, 636 subjects were followed up for 3.3 years, and serum CRP level was associated with LA [56]. In addition, Nam *et al.* [57] found that the ratio of neutrophils to lymphocytes was related to the volume of high signal in white matter. However, there is a contrary conclusion. The results of Lothian birth cohort 1936 showed that CRP, IL-6 and fibrinogen were related to perivascular space, but not to LA [58]. Wilening *et al.* [59] detected inflammatory markers such as C-reactive protein, IL-6 and soluble tumor necrosis factor receptor 1 and 2 in African Americans and European Americans, and found that there was no correlation between the volume of LA and inflammatory markers.

3.5. β-Amyloid Deposition

Amyloid proteins (a β 1-40 and a β 1-42) are produced by the cleavage of amyloid precursor proteins, which can aggregate into fibrous deposits in brain tissue (plate) and vascular wall. Kandel *et al.* [60] found that the volume of La is significantly correlated with a β, and can be used as a preclinical biomarker of Alzheimer's disease. Some studies have found the toxic effect of a β 1-40 on vascular wall. In patients with Alzheimer's disease, mild cognitive impairment and cerebral amyloid angiopathy, a β 1-40 was found to be associated with LA and lacu-

nar infarction, while a β 1-42 was not [61]. Gomis *et al.* [62] also found that a β 1-40 is highly correlated with diffuse small vessel disease (multiple lacunar infarction and LA) in the cohort study of acute lacunar stroke [63] [64]. In the Rotterdam study, Hilal *et al.* [65] measured the plasma a β 1 levels of 1201 subjects in two independent cohorts. The results showed that the increase of plasma a β 1-40 and a β 1-40/a β 1-42 levels were significantly correlated with the increase of LA volume, and a β 1-38, a β 1-40 and a β 1-40/a β 1-42 were significantly correlated with cognitive function, especially memory function.

In addition, the β-peptide of amyloid protein in normal people has different results. The Rotterdam Scan study found that elevated amyloid peptide levels in ApoE ε 4 carriers were highly correlated with silent infarction and increased white matter lesions [66] (Van Dijk *et al.*, 2004). However, the three city Dijon cross-sectional study did not show that amyloid polypeptides in ApoE ε 4 carriers were associated with La or lacunar infarction. However, after 4 years of follow-up, it was found that the decrease of amyloid peptide level was associated with the progress of LA [67].

3.6. Renin Angiotensin System (RAS)

It is an important component of angiotensin-converting enzyme (angiotensin II, angiotensin-converting enzyme) in angiotensin-converting cells (angiotensin-I, angiotensin-converting enzyme, angiotensin-1, ET-1) [68]. Therefore, as a marker of cerebral small vessel disease, a large number of studies have been conducted on RAS to explore the mechanism of RAS on middle-aged hypertension and cognitive impairment or dementia in later years [69]. Although most studies have focused on single nucleotide polymorphisms, there are still a few studies evaluating protein levels or protein activity in this pathway. In the genetique de l'infractus cerebral study, 510 subjects were enrolled. The results showed that plasma Angiotensin Converting Enzyme (ACE) level was associated with multiple lacunar infarction, but not with La [70]. However, after follow-up observation, it was found that the increase of Angiotensin Converting Enzyme (ACE) level was associated with the gradual increase of LA volume, but not with cortical atrophy, suggesting that ace has a dual effect (beneficial/harmful) on brain tissue [71].

4. Genetic Factors of LA

At present, with the development of gene technology, scholars at home and abroad have carried out a lot of research on the genetic factors of La to reveal its biological function and pathogenesis of clinical outcomes. The study on genetic susceptibility of LA is divided into two parts: candidate gene related research and genome-wide association study [8]. Candidate gene related studies have identified many genes related to the biogenesis of LA, such as ApoE [72], Angiotensin Converting Enzyme (ACE), AGT and AGTR1 regulating blood pressure and cerebral blood flow [68] [73], and IL-6 and IL5RA [74] [75], BDNF regulating

nerve regeneration [76], MMP family regulating neuroinflammatory response [77] [78], PON1/NOS3 regulating oxidative stress [75]. Genome wide association studies can not only identify the susceptibility genes of leukoencephalopathy, but also explore its molecular mechanism. Fornage *et al.* [79] reported the meta-analysis of a genome-wide association study of LA. The participants were from non stroke residents in seven European communities. The results showed that among the seven known genes on the long arm of chromosome 17 17q25, six new SNPs were associated with LA, including WBP2, TRIM65, TRIM47, MRPL38, FBF1 and ACOX1, which were mainly related to neuroimmune and inflammatory systems. In addition, in Framingham Heart Study, Hofer *et al.* [80] conducted genome-wide association analysis on seven cohort groups. The results showed that there was no significant correlation between SNPs and the progress of LA in middle-aged and elderly people among common genetic factors. Therefore, it is suggested that the reasons for LA progress should be found in environmental, lifestyle and population biological factors.

At present, there are many controversies about the genetic research of LA. In the metastrike study, 2588 patients with ischemic stroke were analyzed. Six new loci of 17q25 were found to be associated with LA volume of ischemic stroke, and the most relevant site was rs9894383 [81]. In the J-SHIPP study, 1190 asymptomatic elderly people in Japan were enrolled. The 17q25 rs3744028 polymorphism was associated with subcortical white matter hyperintensity, but not with periventricular hyperintensity. However, the risk allele of rs3744028 was associated with reduced cognitive function. Therefore, the genetic variation of 17q25 rs3744028 has a biphasic effect on brain tissue and function [82]. In addition, for the study on the relationship between Notch3 gene and La, Schmidt *et al.* Conducted meta-analysis on 4773 hypertensive community population in charge study, and concluded that four new loci rs1043994, rs10404382, rs10423702, rs1043997 were associated with the severity and progression of LA [83]. However, Rutten-Jacobs *et al.* [84] concluded that the four loci of Notch3 gene were not associated with LA volume [85]. The research on ApoE is also controversial. In Northern Manhattan Study, Willey *et al.* [85] considered the correlation between ApoE modified blood lipid and leukoaraiosis, indicating that this correlation is dependent on genotype and deterioration of long-term lipid mass spectrum. In the Lothian birth cohort 1936 study, 624 Alzheimer's disease patients born in 1936 were included in the study. The results showed that ApoE ε was not associated with the volume of leukoaraiosis [86]. The reason for the above conclusion may be related to the different race and sample size. The SNPs of La are summarized as follows in **Table 1**.

At present, some achievements have been made in LA caused by single gene mutation, such as Notch3; ApoE; COL4A1; homocysteinuria; genetic lesions of arteriovenous thrombosis. However, the Mendelian form of cerebrovascular disease is due to the existence of multiple genes and different molecular mechanisms, resulting in similar clinical and imaging manifestations [115]. Therefore, ex-

ploring a unified pathway can provide new ideas for the treatment of sporadic small vessel disease. The following is a review of LA caused by multiple gene interactions.

Table 1. Single nucleotide polymorphism of table La.

Gene	Site	Biological effect	Ethnic characteristics
TRIM65	rs3744028	Innate immunity, apoptosis	Europe [79]
TRIM47	rs3744017		Europe [79]
	rs1055129		
WBP2	rs11869977	Inflammatory response	Europe [79]
	rs936393	Transcriptional regulation	
COX-2	rs689466	Inflammatory reaction	African American, Brazil [87]
ApoE	rs7412	Regulating blood lipid	Denmark, France, Pittsburgh [72]
	rs42935		[88]
	ε2, ε3, ε4		[89]
	ε2, ε3, ε4		[90]
	ε4		Europe [91] [92] [93]
	ε2, ε4		Europe [94]
Claudin-1	rs9290927	Composition of blood brain barrier	The Republic of Korea [95]
AQP-4	rs9951307	Integrity and function of blood brain barrier	The Republic of Korea [96]
NOTCH3	rs1043994	Vascular smooth muscle hyperplasia	Europe [83]
	rs10404382		
	rs10423702		
	rs1043997		
CETP	rs1800775		Germany [97]
ACE	rs1799752	Regulation of systolic blood pressure and blood flow velocity	UK (white) [68] [98]
	rs4646994		[90]
AGT	rs699		Australia, Rotterdam [73] [99]
AGTR1	rs5186		The Therlands, Rotterdam [73] [100]
			America (White) [101] [102]
AGTR2	C3123A		America (White) [102]
CYP11B	rs1799998		France [103]
F3	rs3917643	Regulation of coagulation function	USA (Non Hispanic White) [78]
MTHFR	rs1801133	DNA and RNA biosynthesis	Japan, Hungary, USA [104]
	rs1801131		[101] [105]
IL-6	rs1800795	Immune and inflammatory response	America (White) [74]
IL-10	rs1800896		India, Greece, Italy [106]
IL5RA	rs2290608		Spain (White) [75]

Continued

ITGB6	rs1049721		Spain (White) [75]
CAPN10	rs7571442		USA (Non Hispanic White) [78]
NR3C1	rs6190		Netherlands [107]
SH3PXD2A	rs12357919	Inflammatory reaction and gliosis	Europe, African American, Spain, Asia [108]
SH3PXD2A	rs7909791		
EFEMP1	rs78857879		
HAAO	rs11679640		
KITLG	rs995029	Proliferation of vascular endothelial cells	USA (Non Hispanic White) [78]
BDNF	rs6265	Nerve regeneration	America [76]
			Taiwan, China [109]
			America (White) [101]
MMP2	rs9928731	Neuroinflammatory reaction	USA (Non Hispanic White) [78]
MMP3	rs679620		Non Hispanic White [77]
MMP9	rs2250889		Non Hispanic White [77]
MMP13	rs2252070		Spain [75]
ICAM1	rs5498	Cytoskeleton and cell adhesion	Europe [79]
KLC1	rs8702		Hungary [110]
ADD1	rs4961	Regulating ion transport and sodium pump	Rotterdam [111]
A2M	rs669	Regulating cerebral blood flow	Spain (White) [75]
PON1	rs854560	Oxidative stress	Australia, Chile [112]
	rs662		[73] [113]
NOS3	rs1799983		Netherlands, Spain (White) [100]
	rs1800779		[75]
FOXF2	rs12204590	Lack of differentiation of vascular parietal cells	Europe [114]

4.1. Genes Related to Blood Pressure Regulation

Adib-Samii [116] conducted genome-wide association analysis on 2336 patients with ischemic stroke and found that hypertension patients were significantly higher than non hypertensive patients in common SNPs of LA, suggesting that hypertension and non hypertension patients may have different genetic structure and pathophysiological mechanism.

4.1.1. Angiotensinogen Gene (AGT)

Angiotensinogen is a member of RAS system. AGT is transformed into angiotensin I by renin, and then angiotensin I is transformed into angiotensin II by angiotensin I converting enzyme. Angiotensin II regulates systolic blood pressure, water salt balance, maintains vascular tension, and increases the levels of vasopressin and adrenocortical hormone in the central nervous system [117]. Angiotensinogen gene is involved in the renin angiotensin aldosterone system in regulating blood pressure, thus participating in the formation of white matter le-

sions. The angiotensinogen gene is located on chromosome 1q42-43 with five exons and a large number of gene polymorphisms. M235T (methionine substituted threonine at residue 235) and T174M (methionine substituted methionine at residue 174) are the two most studied gene polymorphisms. Meta-analysis showed that M235T and T174M gene polymorphisms were associated with ischemic stroke in China [118]. The involvement of AGT gene in the pathogenesis of ischemic stroke is due to the influence of blood pressure [119]. However, a meta-analysis showed that the AGT (M235T) polymorphism did not appear to be associated with high white matter signal [90]. In addition, Salminen *et al.* [120] tested the gene polymorphism of AGT rs699 M235T for healthy elderly people, assessed the integrity of specific white matter fiber bundles by diffusion tensor imaging, and measured the volume and cognitive function score of subcortical white matter lesions. The results showed that M235T variant was not associated with subcortical white matter hyperintensity. The threonine variation of M235T was associated with abnormal white matter tracts and cognitive function, independent of the volume of subcortical white matter lesions.

4.1.2. Angiotensin II Receptor Type 1

Angiotensin II receptor type 1 (AGTR1) gene is located on chromosome 3q21-q25, with more than 20 gene polymorphisms. At present, A1166C (rs5186) is the most frequently studied gene polymorphism of AGTR1, which increases the risk of atherosclerosis, hypertension and ischemic stroke [121]. Taylor *et al.* [102] reported that the variation of C1166 increased the volume of white matter lesions in a group of elderly men over a period of 2 years. The team proposed a similar view in 2013 that C1166 polymorphism was associated with the severity of white matter lesions in some Alzheimer's patients with or without depressive symptoms [101]. In addition, the polymorphism of C1166 may be used as a biological reference marker of brain integrity in some healthy elderly people before cognitive function changes [121].

4.1.3. Angiotensin Converting Enzyme (ACE)

Angiotensin converting enzymegene is located on chromosome 17q23, with a length of 17KB, and more than 100 polymorphisms have been identified. Paternoster *et al.* [90] included 46 studies, 19 candidate gene polymorphisms, and 19,000 patients with ischemic stroke. Meta-analysis showed that Angiotensin Converting Enzyme (ACE) (I/D) may be associated with LA. Another meta-analysis showed that Angiotensin Converting Enzyme (ACE) (I/D) had genetic susceptibility to small vessel disease in Europe [122].

4.1.4. Aldosterone Synthase

Aldosterone synthase is located on chromosome 8q24.3 and consists of nine exons. Brenner *et al.* [70] selected 510 European patients with acute cerebral infarction in the genic study. The results showed that aldosterone synthase CYP11B2 -344C had a protective effect on LA. Another meta-analysis showed that the C allele in the aldosterone synthase gene CYP11B2 T (- 344C) was associated with a

reduced risk of leukoencephalopathy. However, according to Chandra *et al.*, TT, TC, CC of CYP11B2 are not associated with LA induced cognitive impairment [31].

4.1.5. Renin Angiotensin System (RAS)

We have known that LA is most closely related to age and hypertension. Therefore, people pay more attention to the relationship between gene polymorphism of renin angiotensin regulatory system and white matter lesions. Assareh *et al.* [123] compared 445 elderly people aged 60 - 65 years of LA in Australia with healthy elderly people. It was found that any gene polymorphism of AGT rs699, Angiotensin Converting Enzyme (ACE) rs4362 and AGTR1 rs5182 was not associated with La lesions; however, after adjusting blood pressure factors, AGT rs699 gene and AGTR1 rs5182 gene had synergistic effect in the occurrence of LA; after gender stratification, Angiotensin Converting Enzyme (ACE) rs4362 and AGT were found Rs699 was associated with leukoencephalopathy in men, and the two genes still interacted before and after regulating blood pressure. Gormley *et al.* [124] detected 5 sites of AGT and 8 loci of ace. The results showed that there was no correlation between AGT and Angiotensin Converting Enzyme (ACE) and La. However, only in patients with hypertension, the polymorphism of AGT promoter (- 20A → C) is associated with ischemic La subtype. Therefore, it is speculated that the allele of AGT - 20C may be a risk factor for LA in patients with hypertension.

4.2. Homocysteine (MTHFR) Related Genes

MTHFR gene is a folate related enzyme and plays an important role in homocysteine synthesis. MTHFR gene is located on chromosome 1p36.6, and at least 24 polymorphisms have been found so far. The most studied regions of variation include: the variation of cysteine to threonine at 677 bp (C677T, rs1801133) and the variation of alanine to cysteine at 1298 bp (A1298C, rs1801131), both of which lead to hyperhomocysteinemia. Studies have shown that MTHFR C677T is associated with elevated serum homocysteine levels; clustering of MTHFR T 677C and A1298C heterozygous variants is moderately associated with the risk of L. MTHFR A1298C and 1298CC were associated with LA and were independent risk factors. MTHFR A1298C and 1298CC were associated with LA and were independent risk factors [105]. Rutten-Jacobs *et al.* [125] conducted a meta-analysis of the European origin population, showing that MTHFR C677T is associated with lacunar stroke and LA volume, and is associated with hypertension. However, another meta-analysis showed no significant correlation between MTHFR, C677T, homocysteine and LA [126]. A genetic testing study on LA population in southern China did not show that rs1801133 (C677T) and rs1801131 (A1298C) of MTHFR were significantly associated with LA [127].

4.3. Regeneration Related Genes

Brain Derived Neurotrophic Factor (BDNF) is produced by glial cells and plays

an important role in protecting and promoting the regeneration of nerve fibers. BDNF gene is located at the junction of 11p13 and 11p14. The most common variant is valine to methionine (V66M, rs6265), which reduces the production of BDNF. Taylor [76] and others studied the relationship between BDNF Val66Met gene polymorphism and LA in 199 elderly patients with depression. The results showed that BDNF met66 allele was associated with increased LA volume in elderly patients with depression. In addition, it was found that val-66al was related to the short-term memory function of valine in male subjects from Taiwan [109].

4.4. Genes Related to Oxidative Stress

The paraoxonase (PON) family consists of three genes: PON1, PON2 and PON3, which are arranged on chromosome 7. Members of the PON family encode high-density lipoprotein to prevent the development of atherosclerosis [128]. Some studies suggest that PON1 (7q21.3) is associated with LA, while another study suggests that L55M and Q191R (rs854560) are associated with La progression [113].

4.5. Inflammatory Disease Gene

Cyclooxygenase-2 (COX-2) is a key enzyme in the transformation of arachidonic acid into prostaglandins, and prostaglandins are important inflammatory mediators. Shan *et al.* [129] recruited 334 patients with LA and 116 patients with lumen infarction in China to investigate the regulatory effect of COX-2 - 1195G > A (rs689466) and - 765G > C (rs20417) on cerebral small vessel disease. The results showed that the - 1195G > A polymorphism and haplotype A-1195-G-765 of COX-2 were associated with the susceptibility of La in Chinese. CYP2J2 (CYP2J2) 50G > T polymorphism was associated with LA volume and cognitive dysfunction [130].

4.6. Extracellular Matrix Protein Gene

Matrix Metalloproteinase (MMP) is a zinc and calcium dependent endopeptidase secreted by neurons and glial cells [131]. MMP can cleave almost all matrix proteins, which can be inhibited by tissue inhibitor of metalloproteinase. In the Framingham offspring study involving 583 subjects, plasma levels of MMP-9 and MMP-1 inhibitors were associated with La and brain atrophy [132]. Zhang *et al.* [133] found that the single nucleotide polymorphism of MMP-2-1306 in China was directly related to LA.

4.7. Blood Brain Barrier Gene

Blood brain barrier plays an important role in LA, and AQP-4 is related to the progress of La. Studies have shown that the T allele and CT/TT genotype of AQP-4 (rs2075575) are associated with LA, while AQP-4 (rs9951307) is not associated with LA [96]. However, rs9951307AG + GG genotype and rs2075575

CT + 1 TT genotype had synergistic effect on LA, and haplotype C-A was associated with La. It is suggested that the genetic variation and haplotype of AQP-4 may be related to LA.

5. Hemodynamic Changes of LA

At present, scholars at home and abroad have recognized the theory of hemodynamic changes in LA, and have done a lot of research around this point [134] [135] [136] [137]. Due to the characteristic anatomical structure of LA, if combined with age, hypertension, diabetes and other risk factors, cerebral arteriosclerosis and vascular lumen stenosis will gradually occur in LA, which will damage the automatic regulation function of cerebral blood vessels, resulting in corresponding clinical symptoms [8]. The regulation of cerebral blood flow includes three aspects: blood pressure, neurogenic and metabolic regulation. Metabolic regulation is that changes in carbon dioxide metabolism change the diameter of small vessels, that is, cerebrovascular reactivity, that is, the regulatory function of cerebral blood flow is consistent with the metabolic state [138]. It is generally believed that cerebral blood flow velocity changes after vasodilation stimulation, and cerebrovascular reactivity is determined by the ability of these changes [139].

Etherton *et al.* [140] proposed that FLAIR sequence of MRI can present the macroscopic results of white matter, but can not show the microstructure damage of white matter. Using Diffusion Tensor Imaging (DTI), they observed a decrease in the diffusion coefficient anisotropy of normal white matter on the opposite side of the lesion in patients with acute ischemic stroke, which was associated with neurological impairment at 3 months after stroke. Conclusion the integrity of white matter in acute cerebral infarction can predict the prognosis of neurological function after stroke. However, the application of DTI has received many limitations, and TCD is widely used in clinical because of its simplicity and rapidity. Great arteries and microcirculation are communicating channels, so TCD can provide functional status information of related downstream microvessels [135].

In 2014, the study of cerebral blood flow reserve in patients with tgoulis was summarized [41]. This study suggests that the correlation between cognitive impairment and vascular risk factors can be evaluated by observing intracranial hemodynamics. Arba *et al.* [141] pointed out that the cerebral perfusion of patients with acute attack of La has changed and is related to the severity of imaging. Altmann [134] observed that the blood flow velocity of middle cerebral artery decreased and the pulsatility index increased in patients with small vessel disease by transcranial Doppler ultrasound. Turk *et al.* [142] found that the pulsatility index (PI) and Resistance Index (RI) of patients with La were increased, although there was no statistical significance compared with the control group; in addition, they found that the blood flow velocity of middle cerebral artery was decreased and the carotid artery hardness was increased in LA patients com-

pared with the control group, and the combination index of the above two may be used to diagnose LA.

Inharakham *et al.* [143] did breathe holding test for patients with lacunar infarction, and observed the changes in blood flow velocity, heart rate and blood pressure of the middle cerebral artery. The results showed that there were significant differences between the two groups, indicating that the parasympathetic nerve function of patients with lacunar infarction was weakened. Whether this phenomenon is caused by hypertension or whether it needs to be further explored. But there are opposite conclusions, Bohr *et al.* [144] In order to verify that the ability of the autonomic nervous system to maintain the homeostasis of brain physiological function in the elderly is weakened, 45 elderly people (75 - 89 years old) were recruited to perform Valsalva maneuver. The effective transverse relaxation rate R2 (R2 is inversely proportional to the oxygenation level of brain tissue) was evaluated by two-way echo functional Magnetic Resonance (fMRI), and the volume of La was calculated. There was no statistically significant correlation between the two variables after analysis. This study does not support the cumulative effect of autonomic nervous dysfunction on the formation of white matter lesions.

Some studies have shown that after 4 years of follow-up observation, it was found that the occurrence of white matter lesions preceded the gradual decrease of cerebral blood flow [145] [146]. The initial results showed that with the aggravation of white matter lesions, cerebrovascular reactivity decreased. However, Bernbaum *et al.* [147] found that in patients with minor stroke and transient ischemic attack, cerebral blood flow had been reduced before LA, after 3 years of follow-up observation

6. Relationship between LA and Carotid Atherosclerosis

LA is caused by small vascular disease, but the influence of large vascular disease on LA has attracted people's attention. In patients with large artery atherosclerosis, especially carotid atherosclerosis, insufficient cerebral perfusion may affect the severity and prevalence of LA, which is closely related to ischemic stroke [148]. Macrovascular and small vessel lesions often coexist. With the progress of subclinical small vessel disease, asymptomatic large vessel disease gradually worsens, and vice versa [149]. Some studies have even suggested that they may have common genetic components [150]. Ishikawa *et al.* [151] found that the coexistence of carotid plaque and white matter lesions increased in patients with symptomatic cerebral infarction, but such cerebral infarction was not caused by stenosis or occlusion of main cerebral vessels. It indirectly explained the relationship between white matter lesions and carotid plaque. In addition, some studies have pointed out that the volume of LA is related to the attenuation of the CT value of carotid plaque [32]. However, there are many controversies in current studies. A meta-analysis shows that LA is associated with carotid plaque, but not with simple carotid stenosis; in further subgroup analysis, carotid steno-

sis is a protective factor for LA [152]. In addition, a systematic review indicates that there is no definite correlation between the left and right distribution of the cerebral hemisphere in patients with carotid artery stenosis and LA, and further research is needed.

7. Treatment and Clinical Prognosis of LA

Due to the high incidence rate of small cerebral vascular disease, the quality of life of patients has been seriously reduced. So far, there is no specific treatment for preventing cognitive decline after stroke. However, effective treatment for risk factors of vascular diseases, such as platelet aggregation, antihypertensive drugs, statins, and anticoagulation therapy, can control the progress of vascular disease and the obsession with vascular diseases [153]. In a 7-year cohort study (adelahyde-2), angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, statins may have protective effects [154]. Prospective studies are needed to assess the protective effects of these interventions on cognitive function.

In a subgroup analysis of the Scandinavian multi-infarct dementia trial study, nimodipine was effective in subcortical small vessel disease [155]. It is well known that hypertension is a risk factor for LA, so infinity studies have observed that intensive treatment of ambulatory blood pressure in elderly patients can reduce neurological impairment [156] [157]. Nocturnal hypertension has an impact on white matter lesions in elderly patients with hypertension, so it is very important to regulate ambulatory blood pressure [158]. Some studies have shown that the use of rennin-angiotensin II receptor blockers (ARBs) in the treatment of hypertension can control the increase of LA volume and improve the decline of cognitive function compared with other methods [159] [160] [161].

Studies have shown that LA can predict the adverse outcomes of acute and subacute stroke [162]. In addition, mechanical thrombectomy was performed in patients with ischemic stroke with acute anterior circulation occlusion. Moderate and severe LA was associated with adverse outcomes in patients with recanalization [163]. A meta-analysis by Kongbunkiat *et al.* [164] showed that intracranial hemorrhage and adverse events after thrombolysis in patients with acute ischemic stroke were related to the severity of LA. However, La should not be listed as a taboo [165]. It is suggested that patients with La should be given intravascular therapy or reduce the dosage of thrombolytic drugs such as recombinant tissue plasminogen activators to reduce the risk of intracranial hemorrhage after thrombolysis [166].

8. Current Problems and Prospects

At present, there are many controversies about the risk factors and pathogenesis of LA. In addition, there is no final conclusion on the gene research of LA [8], whether the linkage genes obtained from genome-wide association studies are repeatable; in addition, the results of candidate gene association studies have not been confirmed by genome-wide association studies. Therefore, large-scale co-

operative longitudinal cohort studies are needed to further explore the genetic factors of LA. There is no specific treatment for LA patients, and a large number of longitudinal studies are needed to reveal the underlying pathophysiological, hemodynamic and genetic mechanisms.

Authors' Contributions

Professor Xiaoguang Luo is responsible for determining the content of the review and revising the manuscript. Ying Bian is responsible for consulting materials and drafting the manuscript. Yujiao Lin, Xiaofeng Chen, Ying Ma and Yan Liu are responsible for searching for materials.

Project Approval

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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