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Advances in Lacunar Stroke Pathophysiology: A Review

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Abstract

Importance: As the second leading cause of death in the world, stroke has a large societal impact. Nearly one-third of ischemic strokes are lacunar strokes (LS), or small subcortical infarcts. While smaller in size they represent large problems, leaving many patients disabled and demented. Little is known about the underlying etiology of LS, slowing the development of novel therapeutics.

Observations: When the term lacune was described in the 1800s, its underlying pathophysiological basis was obscure. In the 1960s, C. Miller Fisher performed autopsy studies that showed that vessels supplying lacunes displayed segmental arteriolar disorganization, characterized by vessel enlargement, hemorrhage, and fibrinoid deposition. For these pathological changes, he coined the term lipohyalinosis. Apart from these early descriptions of LS and lipohyalinosis, few attempts have been made to reconcile this pathological description with modern mechanisms of cerebral small vessel disease (cSVD).

Conclusions and Relevance: During the last six years, progress has been made in understanding the clinical mechanisms, imaging characteristics, and genetic basis of LS. Questions persist regarding the order of events related to the initiation and progression of cSVD, how LS is related to other sequelae of cSVD, and if LS is part of a systemic disease process. These advances prompt a re-assessment of the current understanding of the etiology of LS and cSVD. The development of targeted therapies depends on a complete understanding of these mechanisms.

Historical Background

Stroke is the second leading cause of death in the world and the leading cause of disability in the United States.[1] Among ischemic strokes there are different subtypes, including large artery atherosclerosis, cardioembolism, and cerebral small vessel disease (cSVD). While cSVD has several clinical and radiographic manifestations, lacunar stroke (LS) is prototypical and accounts for 20–30% of ischemic strokes.[2,3] Clinically, LS can manifest

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with several syndromes depending on lesion location.[4] Silent LS are found in 20–50% of healthy elderly people.[5] LS are particularly burdensome given a 20% recurrence rate, 25% 5-year mortality, and associated morbidities such as vascular cognitive impairment.[3]

LS, appropriately named given their propensity to form cavities (lacunes), were first described in 1838 (Figure 1).[3] More recently, the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) definitions were developed to standardize terms that describe imaging sequelae of cSVD, including recent small subcortical infarcts, lacunes, white matter hyperintensities (WMH), perivascular spaces, microbleeds, and brain atrophy.[6] LS encompasses two terms: recent small subcortical infarcts, defined as recent infarctions in the territory of one perforating arteriole with imaging features or clinical symptoms consistent with occurrence in the previous few weeks, and lacunes, defined as round or ovoid, subcortical, fluid-filled cavities of between 3 mm and about 15 mm in diameter consistent with previous acute small subcortical infarcts or hemorrhages in the territory of one perforating arteriole.[6] While the focus of this review is LS, it is important to appreciate other pathologies that result from cSVD as there are inter-related mechanisms and treatment implications. For example, many intracerebral hemorrhages (ICH) likely result from similar vessel pathology,[7] suggesting that LS patients may be at higher bleeding risk on antithrombotic medications.

In the 1960s, Fisher performed numerous pathological studies showing most LS are found distal to occlusive lesions of small perforating arteries.[4] He used the term lipohyalinosis to describe what he believed was a unique hypertensive cerebral vasculopathy characterized by fibrinoid vessel wall necrosis and segmental arteriolar disorganization. There were three prominent, often overlapping findings: vessel enlargement, hemorrhage, and fibrinoid deposition.[4] Modern classification schemes for sporadic non-amyloid cSVD pathology vary and overlap, including atherosclerosis, microatheroma, arteriosclerosis, arteriolosclerosis, and lipohyalinosis.[8] cSVD affects a range of vessel sizes, from 40–900 μm in diameter.[7] Arteriosclerosis and atherosclerosis affect vessels of 200–800 μm, arteriolosclerosis causes concentric vessel wall thickening in arteries of 40–150 μm, and lipohyalinosis affects vessels of 40–300 μm.[8]

The focus of this review will be LS caused by sporadic non-amyloid cSVD, and we limit discussion of other imaging markers of cSVD. Aside from thrombolysis for acute LS, there has been limited progress in the targeted treatment of this condition compared to other stroke subtypes. These pathologies were traditionally described as resulting from chronic hypertension; despite today's anti-hypertensive agents, LS due to cSVD persists, and its etiology is likely multifactorial.[2] This review discusses progress in understanding the pathogenesis of LS, its imaging characteristics, and its genetic basis. We explore connections between LS and systemic small vessel disease. Lastly, we describe new models and approaches that can be used to study LS and cSVD.

Search Strategy and Selection Criteria

References in the remainder of this review were identified by searches of PubMed from 2012–2017, and references from relevant articles. The search terms "lipohyalinosis AND

lacune" (2 total hits, 0 relevant), "small vessel disease AND lacune" (27,6), "genetics AND lacune" (4,1), "models AND lacune" (10,1), "lipohyalinosis AND lacunar stroke" (12,1), "small vessel disease AND lacunar stroke" (289,59), "genetics AND lacunar stroke" (85,4), "models AND lacunar stroke" (172,6) were used. Articles were independently screened by 2 authors for appropriateness and relevance to the topic. There were no language restrictions.

Clinical Correlations and Underlying Mechanisms

Recent studies suggest that not all LS are attributable to cSVD (Figure 2). Branch atheromatous disease is one proposed etiology involving large artery disease that obstructs the orifices of penetrators.[2] One study showed that a quarter of LS patients had large artery abnormalities on vessel imaging, emphasizing the importance of vessel imaging.[9] Furthermore, a small portion of LS may occur from artery-to-artery embolism. A population-based study showed a relationship between calcium content in the carotid siphon and silent LS.[10] Another study evaluated patients with acute stroke by TEE for aortic atheroma, and LS increased the odds of having aortic plaques.[11]

Cardioembolism may also account for some rare cases of LS. In one study, 11% of patients with symptomatic LS were found to have a possible carotid or cardiac source. LS in the basal ganglia were slightly larger and were three times more likely to have a possible embolic source, but no other risk factors differed with stroke size, shape, or location.[12] Another study examined patients with atrial fibrillation who had either recent LS or non-lacunar stroke. Chronic lacunes were an independent predictor of the incident infarct pattern, suggesting that LS might be caused by intrinsic cSVD despite the presence of concomitant atrial fibrillation.[13] These associations may be due to shared risk factors, such as hypertension, dyslipidemia, and diabetes mellitus (DM).

Recent work in cSVD-related LS has focused on elucidating two pathogenic mechanisms: endothelial dysfunction and blood-brain-barrier (BBB) disruption.[2] While several mechanisms are involved in the sequelae of cSVD, endothelial dysfunction may be the most important for LS. The endothelium regulates vessel tone, regulates fibrinolysis/coagulation, participates in inflammation, and is involved in angiogenesis. Its dysfunction reflects a shift towards a vasoconstrictive, procoagulation, proinflammatory, and proliferative balance.[14] The details of this shift remain largely unknown and likely result from a complex interplay of aging, oxidative stress, mechanical stress, genetic predisposition, and other risk factors such as hypertension. The endothelium incurs structural and functional damage, becoming leaky and inflamed. Further damage leads to impaired autoregulation, where the vessel is unable vasodilate to maintain perfusion.[15] The vessel wall thickens as connective tissue replaces normal wall layers with ultimate lumen narrowing, thrombosis, and occlusion.[2] A recent study examining the endothelium of small penetrating arteries showed that thrombomodulin, a marker of endothelial dysfunction, was elevated in brains with cSVD compared to aged controls.[16] Vascular endothelial growth factor has also been examined as a contributor to cSVD proliferation. In one recent study, however, it was not associated with cSVD severity.[17] Recently, brains with pathologic evidence of cSVD were utilized to show an impaired vasodilator function of white matter penetrating arterioles compared to pial

arterioles. Furthermore, areas of white matter injury were associated with decreased mature oligodendrocytes, suggesting impaired myelination.[18]

In addition to endothelial dysfunction, BBB degradation is thought to play a critical role in cSVD and LS. There is also overlap with the pathogenesis of WMH, as edema that develops surrounding leaky vessels can cause gliosis and appear as WMH on imaging. The BBB is composed of inter-related structures, including endothelial cells joined by tight junctions, basement membranes, associated perivascular spaces, pericytes, glia limitans, and astrocyte end feet.[15] In one study to assess BBB permeability, patients with nondisabling LS or cortical strokes (controls) underwent contrast-enhanced magnetic resonance imaging (MRI) acutely and then again in 3 years. Poor functional outcome was associated with increased basal ganglia BBB permeability.[19] More recently the same group demonstrated further evidence that BBB leakage mediates cSVD, and the severity of leakage was associated with hypertension.[20] Another study confirmed global cSVD burden is associated with increased BBB degradation in both the acute LS and non-ischemic areas.[21]

Improved Understanding through Imaging

Recent advances in ultrasonography, such as transcranial Doppler (TCD), have provided insight into understanding LS and cSVD. One TCD parameter, the pulsatility index (PI), reflects distal cerebral vascular resistance and is posited to be a surrogate marker of cSVD. In a study of patients with acute LS who underwent TCD and MRI, PI was associated with infarct volume.[22] An additional parameter assessable by TCD is dynamic cerebral autoregulation. A small study of unilateral LS patients showed that even though strokes were unilateral, there were bilateral impairments in autoregulation even 6 months after stroke,[23] suggesting the presence of global pathology.

Computed Tomography (CT) studies also shed light on the underlying pathophysiology and role of hypoperfusion in LS and cSVD. In a study using CT perfusion, acute LS showed a smaller perfusion deficit compared to cortical strokes,[9] supporting a focal small vessel pathology. However, another study showed that hypoperfusion of white matter remote to acute infarcts was associated with LS compared to other stoke subtypes, further supporting a global pathology.[24] In a comparison of WMH to contralateral white matter, one study showed WMH had decreased cerebral blood flow (CBF) and decreased vascular reactivity.[25] Another study compared baseline and 4-year follow-up MRIs in patients with LS; baseline WMH volumes were associated with decline in CBF over time, but baseline CBF was not associated with progression of WMH or LS.[26] However, another study of minor strokes compared MRIs at baseline to those after 18 months, and regions with low baseline CBF were associated with the development of new WMH.[27] There are conflicting data about whether or not lower CBF predates WMH and LS development,[28] but this hypothesis is favored.

Advancements in MRI technology have dramatically improved the clinical phenotyping of LS. For example, since the advent of MRI, heritability estimates for lacunar stroke were markedly increased compared to prior studies using CT and clinical exam.[29] Furthermore, MRI has increased the ability to detect cSVD markers, including cerebral microinfarcts

(CMI).[30] CMI, at 0.2–3 mm in size, are smaller than lacunes at 3–15 mm. Another distinction between CMI and LS is their presence throughout the brain including the cortex. While deep CMI are likely secondary to non-amyloid cSVD,[31,32] cortical CMI are more heterogeneous in etiology as they are related to cerebral amyloid angiopathy,[31,32] non-amyloid cSVD and LS,[30] and intracranial stenosis and large cortical infarcts.[30] New techniques are also being developed, including overlapping small vessel templates on MRI images. One study categorized first, second, and third-order branch infarcts, and as vessel branch order increased (smaller vessel), the size of LS decreased.[33]

Longitudinal changes can be seen in many cSVD MRI surrogates, including LS, demonstrating these involve dynamic processes.[34] Recent studies showed that some acute LS can become undetectable on repeat imaging[35] and some WMH can regress after minor stroke.[36] Several imaging studies show a relationship between LS and WMH (Figure 3). A study using advanced MRI techniques identified incident LS and showed they have a predilection for the edge of WMH, supporting the concept of a WMH “penumbra”.[37] However, another study of incident LS showed that their main axes and planes aligned with the orientation of perforating arteries and not with fiber tracts.[38] This supports the presumed vascular etiology, despite the predilection for forming near the edge of existing WMH.

Advancements in Understanding Genetics

Although LS is a multifactorial disease, there are considerable differences in susceptibility to risk factors when comparing individuals. Family history of vascular disease is an independent risk factor for LS, and twin and family studies show that cSVD has a genetic basis.[39] In addition, there are several single gene disorders that precipitate familial cSVD, which accounts for 1–5% of all strokes.[39] Although the contribution of individual genes in developing sporadic cSVD is unknown, a more complete understanding of familial cSVD may provide insight into its pathogenesis. Mutations resulting in familial cSVD are highly penetrant and involve *NOTCH3, HTRA1, TREX1, GLA, COL4A1, COL4A2, FOXC1*, and *PITX2*.[40] Single nucleotide polymorphisms (SNPs) in *COL4A2* have been associated with cSVD-related sequalae,[41] and variants of *COL3A1* have been shown to influence LS recurrence and mortality.[42] Mutations in *COL4A1* have also been identified in patients with ICH.[43] In another analysis, loci in *COL4A2* and *HTRA1* were found to be associated with both LS and deep ICH, supporting a common mechanism.[44]

Although early genetic studies of stroke have many of the same pitfalls as those of other multifactorial diseases, some important genes were implicated using candidate gene studies. These employ the use of SNP analysis in genes that are suspected to play a role in the disease. A meta-analysis showed the *ACE* I/D polymorphism was associated with LS, although larger studies have not replicated this finding.[45] Several studies examined *MTHFR* C677T, showing it is also associated with the development of cSVD.[46] *ApoE* has also been studied in elderly individuals, where *ApoE4* carriers were found to have significantly more cSVD and increased progression of WMH on subsequent MRIs. This may be due to increased Aβ deposition,[47] though other studies suggest *ApoE4* acts through other mechanisms.[48] Interestingly, a recent study has shown a correlation between autosomal dominant Alzheimer’s disease and increased WMH, even before expected symptom onset.[49]

Genome wide association studies (GWAS) represent a powerful non-hypothesis based approach that allows the simultaneous genotyping of more than one million polymorphisms across the genome. In one study of early-onset LS patients, two subtypes were defined: isolated LS and multiple LS with leukoaraiosis.[29] There was significant heritability of these subtypes, suggesting they may be distinct entities. A subsequent study showed that oxidative phosphorylation pathways were associated with multiple LS with leukoaraiosis but not isolated LS.[50] In another study, the rs12445022 SNP was found to be associated with LS.[51] A study examining WMH volume, instead of LS specifically, found several associated SNPs involving the genes *TRIM65* and *TRIM47*.[52] Yet another study of WMH volume found further associated SNPs, including some in genes implicated in Alzheimer's disease and ICH.[53]

One potential drawback to GWAS is that these studies are underpowered to detect rare variants. Whole-exome sequencing (WES) using next-generation technology allows for the rapid sequencing of entire coding sequences. A study in the Chinese Han population showed that SNPs in *C1ORF156*and *XYLB* were related to ischemic stroke.[54] The former variant may carry some importance in patients without hypertension or DM, while the latter may be important in patients with hypertension but without DM. Another small WES study identified two genes, *CSN3* and *HLA-DPB1*, that were unique to patients with LS; *CSN3* has also been implicated in coronary disease and DM.[55] In another WES study, a gene implicated in Charcot-Marie-Tooth disease, *SH3TC1*, was related to WMH.[56] The genetics of LS will be advanced by the Small Vessel and Lacunar Project, an ongoing large, prospective study utilizing next generation sequencing.[57]

Relationship to Systemic Small Vessel Disease

Growing evidence supports a connection between cSVD and other systemic disease processes. As with the theory that some LS are secondary to emboli, it is important to recognize that the associations discussed here may be due to shared risk factors. One study compared cerebral, carotid, and brachial vasoreactivity in patients with recent LS. Patients with LS had more severely impaired cerebral vasoreactivity one month after stroke; the only extracranial vasoreactivity measure that correlated with brain parenchymal abnormalities was brachial endothelial-independent vasodilation.[58] Systemic arterial stiffness has also been evaluated for an association with cSVD. Arterial stiffness can be approximated by ankle-brachial index (ABI), pulse wave velocity (PWV, aortic [aPWV], brachial-ankle [baPWV], and carotid-femoral), cardio-ankle vascular index (CAVI), and augmentation index. One study comparing these parameters for different stroke subtypes showed that ABI was lower in large artery atherosclerosis compared to LS and controls, baPWV was higher in both large artery atherosclerosis and LS compared to controls, and CAVI increased in the order of controls, LS, and large artery atherosclerosis.[59] A different study showed patients with ABI<0.90 and >1.4 were almost four times more likely to have silent LS.[60] In a population-based study, higher aPWV was associated with larger WMH volumes.[61] Silent LS were associated with second peak systolic blood pressure wall tension and end diastolic wall tension independently of arterial stiffness in yet another study.[62]

Additional research has focused on comparing cSVD to pathology in the small vessels of other organs, including the kidneys and retina. There are anatomic and functional similarities as all are small, short vessels that arise from arteries under high pressure. A recent meta-analysis explored this relationship and found an association between worsening renal impairment and asymptomatic cSVD but not symptomatic LS, after controlling for hypertension.[63] However, in a cohort from the Rotterdam Study, worsening renal function correlated with higher prevalence of LS.[64] Two studies of first-ever LS patients showed worsening renal function was associated with increasing overall burden of cSVD.[65,66] In addition to kidney disease, retinal disease may also be related to cSVD, especially in patients with DM. Although there are conflicting results,[67] one study of patients without DM who had either acute ICH or LS showed that both were associated with retinal disease.[68] More investigation is needed to better understand these complex relationships. It is surprising that cSVD would only affect the cerebral vasculature as Fisher speculated, but a definitive link to other organs has been elusive.

Challenges and Opportunities

In summary, not all clinical and imaging defined LS result from cSVD, and this distinction is important for patient treatment approaches and future research. Through mechanisms related to aging, oxidative stress, mechanical stress, genetic predisposition, and other risk factors such as hypertension, the endothelium in cSVD becomes damaged, both in structure and function. The BBB degrades allowing leakage of blood contents, contributing to gliosis and the formation of WMH. Autoregulation also fails which decreases blood flow as vessels cannot appropriately dilate. Focal narrowing due to thickening of vessel walls further contributes to decreased flow; ischemia may lead to WMH and, when areas of focal narrowing become completely occluded, LS. There are conflicting data about whether or not lower CBF predates WMH and LS development, but this stands to reason mechanistically.

While we limit discussion of other sequelae of cSVD, it is clear there is a dynamic interaction between LS, WMH, and CMI. Incident LS can occur in a WMH “penumbra”, and high order vessel disease may be involved in CMI. Perhaps flow-limiting lesions affecting lower-order branched vessels contribute to hypoperfusion distally. When subsequent branches develop worsening pathology and/or when perfusion decreases further in these already vulnerable areas, LS occur and WMH progress. These processes are dynamic, where LS can become undetectable and WMH can regress, occurring through a balance of blood flow changes, focal cSVD changes, and parenchymal repair processes (Figure 4).

Several knowledge gaps need to be addressed. Future studies should focus on the initiation and progression of both the vessel and parenchymal pathology. What are the relative roles of aging, oxidative stress, mechanical stress, genetic predisposition, and other vascular risk factors? Autopsy studies comparing present day cSVD pathology to the lipohyalinosis of Fisher’s time may yield insight as hypertension is better controlled today. Are fibrinoid deposition and necrosis as prevalent as they once were? Has cSVD evolved over time? Furthermore, the time dependent order of events needs to be confirmed in more controlled experiments. Is there evidence of these injury mechanisms before BBB degradation and

endothelial dysfunction? Does this cause decreased blood flow and ischemia? Does functional damage precede the pathologic vessel thickening? While progress has been made understanding endothelial dysfunction, future work on the role of media and adventitial dysfunction, including mechanisms of bleeding and perivascular leakage, may prove fruitful. Recent advances in mapping the brain vasculome may generate new hypotheses.[69] Detailed gene and protein expression profiles for endothelium and perivascular cells may show how function is regulated at different levels of the vascular tree and how homeostasis is affected by co-morbidities and disease. Questions about the best therapeutics persist and may offer further insight into mechanism. Are phosphodiesterase inhibitors more effective than other antiplatelet agents? Does the presence of headache or augmentation of CBF after their use predict effectiveness? Do statins have a salutary effect on the endothelium in cSVD? Even more importantly, what are new therapeutic targets?

For many of these basic questions, experimental models may enhance our understanding. However, they should be chosen carefully as none perfectly mimics the human condition; consideration of several models in complementary fashion may be worthwhile. A recent analysis discussed three main categories of cSVD models: chronically hypertensive animals, chronically hypoperfused animals, and animals that undergo targeted small focal infarcts.[70] One chronically hypertensive model is the stroke-pone Spontaneously Hypertensive Rat,[71] which shares several features with the human condition such as BBB degradation and impaired vascular reactivity. Bilateral carotid artery occlusion is the most common model of hypoperfusion, which ultimately causes white matter injury.[72] For targeted focal infarcts, laser coagulation models and stereotactic injection of vasoconstrictors, such as endothelin-1[73] or N5-(1-iminoethyl)-L-ornithine[74] can be used. These focal infarcts can be targeted to the subcortical white matter, creating lesions that induce a phenotype of hemiparesis similar to human LS.[74] Transgenic mouse models are also utilized; *COL4A1/2* models replicate cSVD,[43] while *Notch* models exhibit WMH with minimal vessel pathology.[40] Lastly, *in vitro* models of oligodendrocytes and blood brain barrier also exist.[75]

While experimental models will provide the opportunity to ask certain questions that cannot be tested in humans, advances in the clinical science of this field continue to move forward. Translation and reverse translation will be important for future research efforts. Recent progress in understanding these disease processes at the clinical level has been made through advancements in imaging and genetics. Currently, there are few targeted treatments for LS. In the future, therapeutics aimed at targeting cSVD mechanisms and white matter injury and repair are urgently needed.

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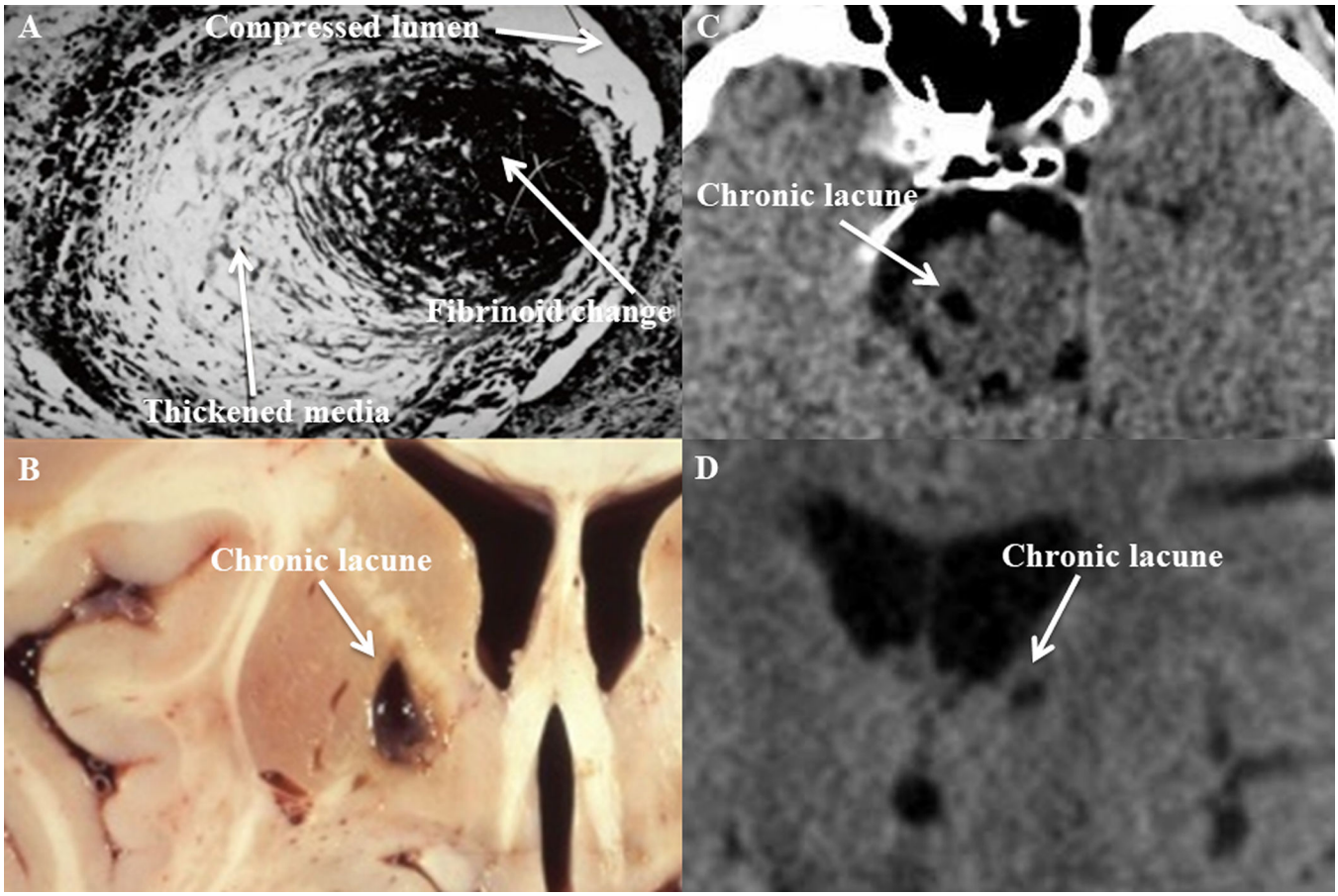

Figure 1. Cerebral small vessel disease (cSVD) histopathological section, lacunar stroke gross section, and lacunar stroke computed tomography (CT) images.

Photomicrograph of cSVD affecting a small penetrating artery (A), showing thickened media and fibrinoid necrosis (Gift from Dr. C. Miller Fisher). Photograph of a cavity secondary to a chronic lacune in the medial basal ganglia (B) found at autopsy.[2] CT images showing hypodensities secondary to chronic lacunes involving the right paramedian pons (C) and left thalamus (D).

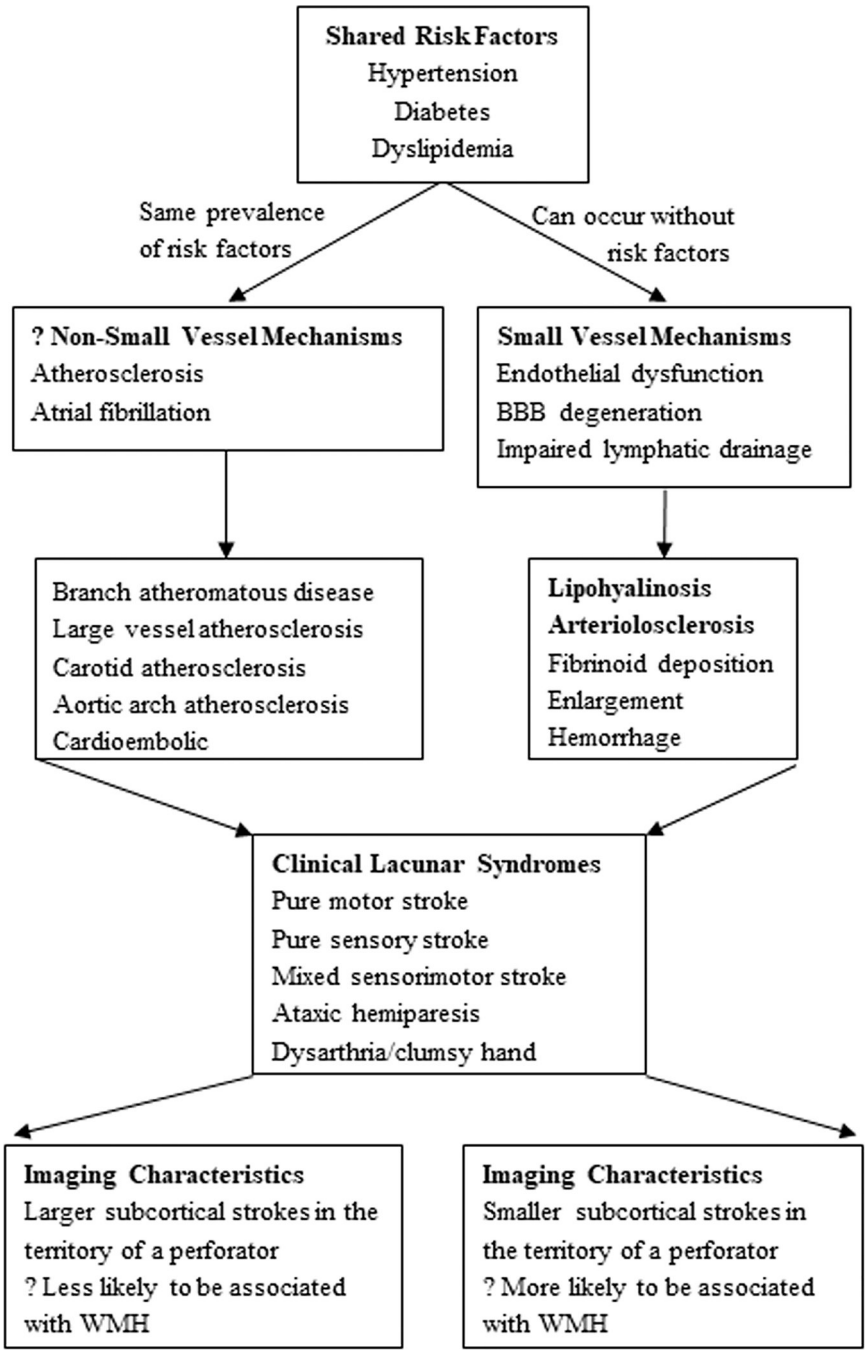

Figure 2. Etiology and clinical phenotype of lacunar stroke (LS).

LS results most commonly from small vessel mechanisms, but alternative mechanisms are feasible. Shared risk factors make many studies difficult to interpret. While the clinical lacunar syndromes are identical, there may be subtle differences in imaging characteristics but meaningful differences in treatment approaches based on etiology. BBB (blood brain barrier), WMH (white matter hyperintensity).

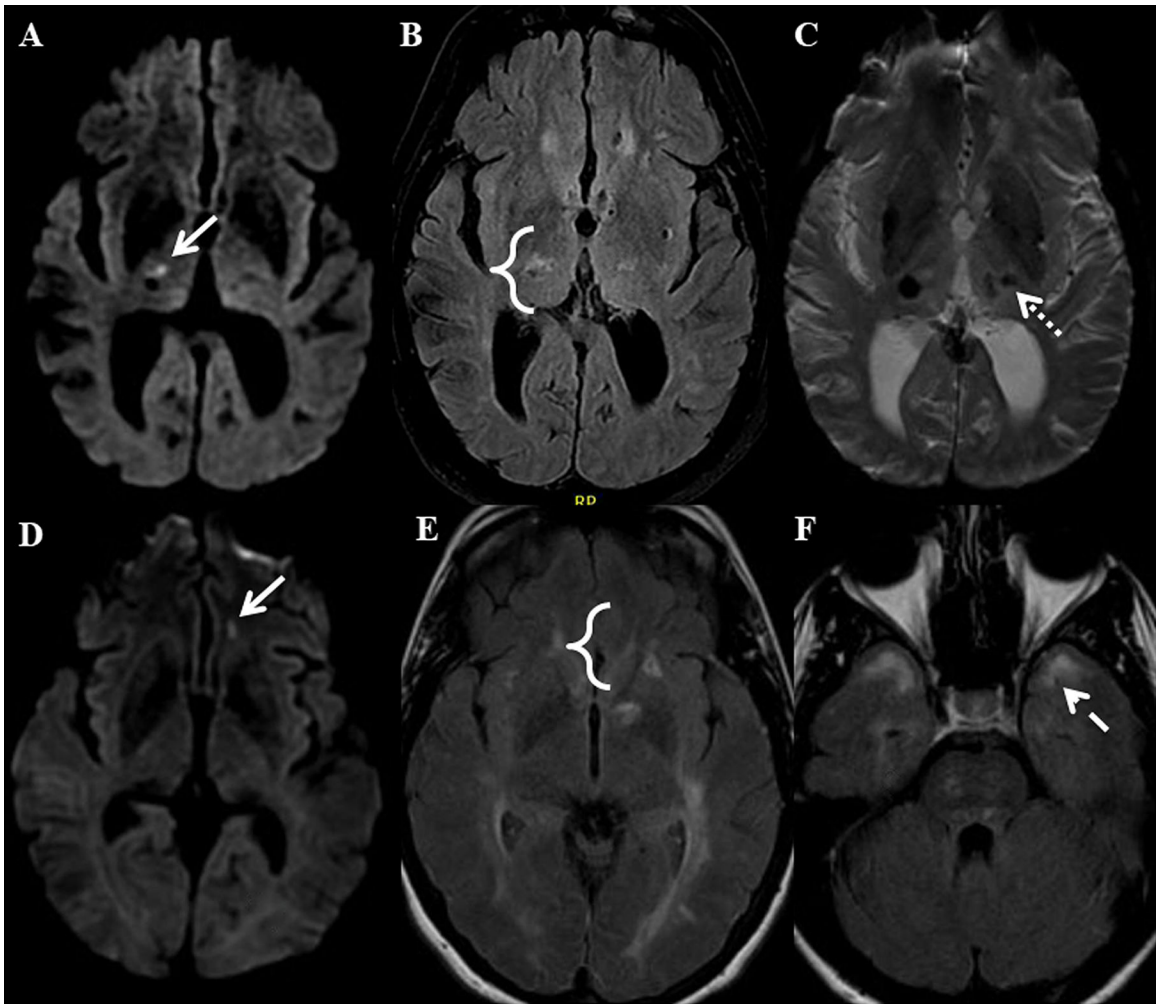

Figure 3. Lacunar stroke (LS) and white matter hyperintensity (WMH) proximity.

Panels A-C show the brain of a patient with severe sporadic hypertension-related cerebral small vessel disease (cSVD). An acute LS (arrow) is shown in the right thalamus on DWI imaging (A). FLAIR imaging (B) shows there is an adjacent WMH (bracket). SWI imaging (C) shows there is also a microhemorrhage in the left thalamus (dotted arrow). Panels D-F show the brain of a patient with CADASIL. An acute LS (arrow) is shown in the left orbitofrontal white matter on DWI imaging (D). FLAIR imaging (E) shows there is an adjacent WMH (bracket). WMH in the anterior temporal lobe (dashed arrow) is also present on FLAIR imaging (F).

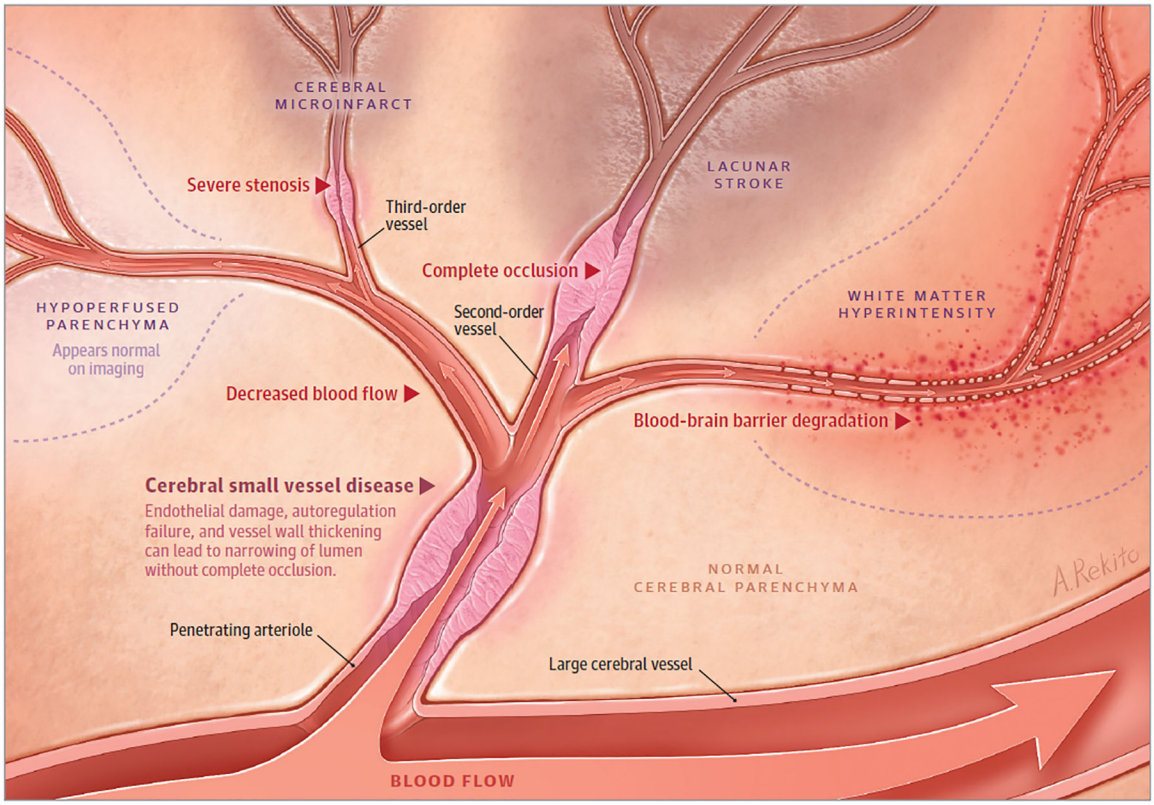

Figure 4.

Originating from a large vessel, a penetrating arteriole is shown with narrowing and impaired autoregulation from cerebral small vessel disease. Downstream, there is hypoperfused parenchyma that appears normal on imaging. In the setting of occluded cerebral small vessel disease in a second-order vessel, lacunar stroke occurs. In higher-order vessels with occluded cerebral small vessel disease, smaller lacunar strokes and cerebral microinfarcts occur. Areas of blood-brain barrier degradation with decreased cerebral blood flow result in white matter hyperintensity. Lacunar strokes align with penetrating vessels, but they also have a predilection to form at the edge of white matter hyperintensities. Hypoperfused parenchyma can progress to lacunar stroke and white matter hyperintensity, although these sequelae of cerebral small vessel disease can also improve over time. The dynamic nature of lacunar stroke likely results from a balance of blood flow changes, focal cerebral small vessel disease changes, and parenchymal repair processes.

Table 1.

Recent genetic studies of lacunar stroke (LS) and cerebral small vessel disease (cSVD).

SNP (single nucleotide polymorphism), GWAS (genome wide association study), WES (whole exome sequencing), ICH (intracerebral hemorrhage), WMH (white matter hyperintensity).

Study Type	Related Gene	Biomarker Studied	SNP	Locus
Single Gene[43]	*COL4A1*	LS, ICH	rs515201	13q34
Single Gene[44]	*COL4A2*	LS, ICH	rs4771674	13q34
Single Gene[42]	*COL3A1*	LS	rs1800255	2q32.2
Single Gene[44]	*HTRA1*	LS, ICH	rs79043147	10q26.13
Single Gene[45]	*ACE*	LS	rs464994	17q23.3
Single Gene[46]	*MTHFR*	LS, WMH	rs1801133	1p36.22
Single Gene[47]	*APOE*	WMH	rs429358	19q13.32
GWAS[51]	*ZCCH14*	LS, WHM	rs12445022	16q24.2
GWAS[52]	*TRIM65*	WMH	rs3744028	17q25
GWAS[52]	*TRIM47*	WMH	rs1055129	17q25
GWAS[52]	*PMF1*	WMH	rs1052053	1q22
GWAS[53]	*SH3PXD2A*	WMH	rs12357919	10q24.33
GWAS[53]	*HAAO*	WMH	rs11679640	2p21
GWAS[53]	*PMF1-BGLAP*	WMH	rs2984613	1q22
GWAS[53]	*EFEMP1*	WMH	rs78857879	2p16.1
WES[54]	*C1ORF156*	Stroke	rs1048177	1q24.2
WES[54]	*XYLB*	Stroke	rs17118	3p21.3
WES[55]	*CSN3*	LS	N/A	4q13.3
WES[55]	*HLA-DPB1*	LS	N/A	6p21.32
WES[56]	*SH3TC1*	WMH	N/A	4p16.1