Brain imaging biomarkers of carotid artery disease

Hediyeh Baradaran[1], Ajay Gupta[2,3]

[1]Department of Radiology, University of Utah, Salt Lake City, UT, USA; [2]Department of Radiology, [3]Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, New York, NY, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: H Baradaran; (III) Provision of study materials or patients: H Baradaran; (IV) Collection and assembly of data: H Baradaran; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Hediyeh Baradaran, MD. 30 N 1900 E #1A141, Salt Lake City, UT 84135, USA. Email: hediyeh.baradaran@hsc.utah.edu.

Abstract: Extracranial carotid artery atherosclerotic disease is a major contributor to ischemic stroke. Carotid atherosclerotic disease can present with a spectrum of findings ranging from mild carotid intima-media thickness to high-risk vulnerable carotid plaque features and carotid stenosis. Before leading to clinically overt stroke or transient ischemic attack, there may be other markers of downstream ischemia secondary to carotid atherosclerotic disease. In this review article, we will review some of the imaging findings that may be seen downstream to carotid artery disease on various imaging modalities, including hemodynamic and perfusional abnormalities which may be seen on CT, MR, or using other advanced imaging techniques, white matter hyperintensities on brain imaging, silent or covert brain infarctions, cerebral microbleeds, and regional and generalized cerebral volume loss. Many of these imaging findings are seen routinely on brain magnetic resonance imaging in patients without overt clinical symptoms. Despite frequently being asymptomatic, many of these imaging findings are also strongly associated with increased risk of future stroke, cognitive impairment, and even mortality. We will review the existing evidence underpinning the associations between these frequently encountered imaging findings and carotid artery atherosclerotic disease. Future validation of these imaging findings could lead to them being powerful biomarkers of cerebrovascular health.

Keywords: Carotid artery diseases; cerebrovascular disorders; cognitive dysfunction; magnetic resonance imaging; stroke

Submitted Feb 26, 2020. Accepted for publication May 10, 2020.
doi: 10.21037/atm-20-1939
View this article at: http://dx.doi.org/10.21037/atm-20-1939

Introduction

Carotid artery atherosclerosis is an established risk factor for cerebrovascular disease and stroke (1,2). In addition to directly causing ischemic stroke, there are many additional deleterious downstream effects of carotid artery atherosclerosis that may be more covert but, nonetheless, are major contributors to patient morbidity and mortality. While these "silent" markers of carotid artery disease may not produce overt or easily identifiable clinical consequences, such as a large ischemic stroke, many are apparent on routine neurological imaging, often in asymptomatic patients. These findings can be seen on a variety of imaging examinations ranging from routine head CT or brain MR to advanced imaging techniques, including CT or MR perfusion or nuclear medicine techniques. Although some of these findings may be seen in otherwise asymptomatic patients, their presence may indicate cerebrovascular compromise, increased risk for future or recurrent stroke, or increased risk for vascular cognitive impairment (3-8). The downstream impact of extracranial carotid disease may be secondary to a wide variety of carotid disease phenotypes, ranging from mild increases in carotid intima media thickness to stenotic carotid plaques with high-risk features (9-13). While the degree of stenosis and features of the carotid plaque itself are critical factors to

Table 1 Summary of imaging biomarkers of carotid atherosclerosis

Imaging biomarker	Definition	Imaging technique	Associated risk
Cerebrovascular reserve (CVR)	Ability of vessels to vasodilate in the setting of reduced cerebral perfusion pressure	CT or MR perfusion, ASL, PET, SPECT, Transcranial Doppler[#]	Impaired CVR is associated with increased risk of future stroke, even in asymptomatic patients
White matter hyperintensities (WMH)	T2/FLAIR hyperintensities in the periventricular and subcortical white matter	Measured both quantitatively and qualitatively, most commonly on MR but can be seen on CT	WMH associated with increased risk of stroke, cognitive decline, dementia, and death
Silent brain infarctions	Infarctions identified on MR without overt clinical symptoms	Seen on MR as either lacunar cavitary infarctions with CSF signal on all pulse sequences or cortical infarctions	Associated with increased risk of stroke, dementia, and cognitive impairment
Cerebral microbleeds	Small hemosiderin deposits from microvascular leakage	T2*-weighted gradient echo or susceptibility images on MR	Associated with increased risk of ischemic infarctions, intracerebral hemorrhage, cognitive impairment, and dementia
Brain volume	Total or hippocampal brain volume	Measured on volumetric MR sequences	Associated with cognitive decline, dementia, and cerebrovascular disease

[#], this can use vasodilatory stimulus such as acetazolamide.

consider when making treatment decisions in patients with carotid artery disease, other imaging findings downstream from the carotid artery disease may also indicate additional "silent" effects of carotid artery disease (14-16). We will review brain imaging findings on both routine and advanced imaging that are associated with carotid artery atherosclerosis.

Mechanisms

Extracranial atherosclerotic disease accounts for 15–20% of all ischemic strokes (17). There are two main pathways for which strokes and transient ischemic attacks occur in patients with carotid artery disease (18). First, a stenosing plaque can limit downstream cerebral blood flow, resulting in hemodynamic alterations, hypoperfusion and potentially hypoxia and infarction. It is for this reason high-grade carotid stenosis is a well-established risk factor for stroke and why carotid endarterectomies are generally recommended for symptomatic patients with high-grade stenosis (19). In addition, the degree of carotid stenosis has long been included as the major determinant of treatment decisions for patients with carotid artery disease, at least in part, because it has served as the dominant inclusion criteria in multiple clinical trials (16,20).

Alternatively, the carotid plaque itself may lead to an artery-to-artery thromboembolic event, resulting in infarction. High-risk plaque features including intraplaque hemorrhage, lipid rich necrotic core, plaque ulceration and other surface irregularities can lead to emboli extending from the plaque surface to distal cerebral arteries or arterioles (15,21). The microembolic phenomena resulting from high risk plaque features has become an important consideration in evaluating patients at high-risk for stroke. These high-risk plaque features can be characterized with both routine and advanced imaging techniques.

It is likely that a significant proportion of ischemic strokes secondary to carotid disease arise from a synergy between hemodynamic and embolic risk factors, since impaired perfusion from flow limitations from a stenosing plaque may make an embolic event that may have been transient, into a cerebral infarction (18). These mechanisms which individually and together account for a large number of ischemic strokes also contribute to structural and microstructural changes to the brain which are evident on imaging but may be difficult to detect clinically (*Table 1*).

Markers of hemodynamic and perfusional abnormalities

One of the most direct methods by which carotid artery disease may cause downstream effects is through the hypoperfusion secondary to stenotic or turbulent flow from flow-limiting plaque (18). Many hemodynamic risk factors

are associated with stroke in carotid artery disease including impairment of cerebrovascular reserve and increased oxygen extraction fraction (7,8). Imaging measurements of hemodynamic alterations downstream from carotid artery disease have been studied as a potential biomarker for increased risk of cerebrovascular disease, even in asymptomatic patients (22,23). Severe, flow-limiting carotid stenosis results in a reduction in cerebral perfusion pressure. In response to a reduced perfusion pressure, cerebral blood flow may be maintained by (I) vasodilation of the cerebral vasculature and/or (II) increase in oxygen extraction (24). When faced with constant reductions in perfusion pressure, vessel autoregulation will lead to maximal dilatation to maintain cerebral blood flow so with any further reduction in cerebral blood flow, there is an increased risk for stroke.

Cerebrovascular reserve is a measure of the ability of vessels to vasodilate when faced with reduced cerebral perfusion pressure (25). There are two main methods for measuring cerebrovascular reserve (7). First, imaging may attempt to directly measure cerebral blood flow to the brain with flow-sensitive imaging techniques including positron emission tomography, other nuclear medicine techniques, CT or MR perfusion both before and after a vasodilatory stimulus (26,27). This approach directly measures CBF at a tissue level. Alternatively, transcranial Doppler can measure flow velocities distal to an area of stenosis or occlusion both before and after a vasodilatory stimulus (23,28,29). Vasodilatory stimuli may be increasing CO_2 levels with breath-holding or inhalation of CO_2 gases (30) or with pharmacologic methods, such as acetazolamide (22,31).

CT perfusion (CTP) is a well-studied and straightforward method for assessing cerebrovascular reserve. Studies have shown that asymptomatic patients with carotid artery stenosis who have abnormal cerebrovascular reserve on CTP are more likely to develop ipsilateral ischemic events (32). In addition, studies have found that hemodynamic changes on CTP can be reversed with carotid artery stenting in both symptomatic and asymptomatic patients (*Figure 1*) (33-35). Though CTP is widely available, the risks associated with radiation exposure and the need for iodinated contrast limit its ability to be widely used as a screening examination. There are also a number of MR based examinations which can be used to evaluate cerebrovascular hemodynamics and perfusion in the setting of carotid artery stenosis. MR perfusion can be measured with dynamic susceptibility contrast perfusion imaging which uses a T2*-weighted echo planar sequence after the administration of intravenous contrast to measure various perfusion parameters. Findings are variable, but many believe that high-grade stenosis may result in elevated MTT (36). Another popular method for measuring MR perfusion is arterial spin labeling (ASL) which can measure perfusion non-invasively, without intravenous contrast by using magnetically-labeled water protons in flowing blood as a tracer. ASL can characterize CBF in patients with ICA occlusion (37) and identify deficits in cerebrovascular reserve in patients with ICA stenosis (38) and occlusion (39).

A comprehensive systematic review and meta-analysis of 13 studies using transcranial Doppler or nuclear medicine techniques to study cerebrovascular reserve with almost 1,000 patients found that there was a significant positive relationship between impaired cerebrovascular reserve and development of future stroke [odds ratio (OR) 3.86; 95% confidence interval (CI), 1.99–7.48] (7). Importantly, this statistically significant relationship persisted with asymptomatic patients, meaning that even completely asymptomatic patients with carotid artery disease who demonstrated impairment in their cerebrovascular reserve were at a higher risk of developing a future stroke.

Positron emission tomography (PET) based measures of cerebral hemodyn amics including measuring oxygen extraction fraction (OEF) using ^{15}O can also be used to measure hemodynamic alterations in the setting of carotid artery stenosis. In the setting of severe carotid stenosis and a reduction in cerebral blood flow, there may be a compensatory increase in oxygen extraction (so called "misery perfusion"). This is thought to occur mostly in end-stages of hemodynamic failure so is usually more pronounced in already symptomatic patients. Indeed, in patients with high-grade carotid artery stenosis (≥70%), a systematic review and meta-analysis found a significant positive relationship between abnormal oxygen extraction and future ipsilateral stroke (OR 6.04; 95% CI, 2.58–14.12) (8). A study of asymptomatic patients did not find a significant association between increased OEF and future stroke (40). While measuring OEF may not be the most effective method for assessing asymptomatic patients with carotid artery stenosis, it can be a tool to identify those who are experiencing end-stage hemodynamic alterations and may be at higher risk for future cerebrovascular ischemia. It also further highlights the downstream hemodynamic alterations experienced in patients with steno-occlusive carotid artery disease. Although using O^{15} methods can be difficult to implement in clinical practice, significant efforts are underway to develop MRI-based techniques to measure the cerebral metabolic rate of oxygen ($CMRO^2$) and OEF as imaging

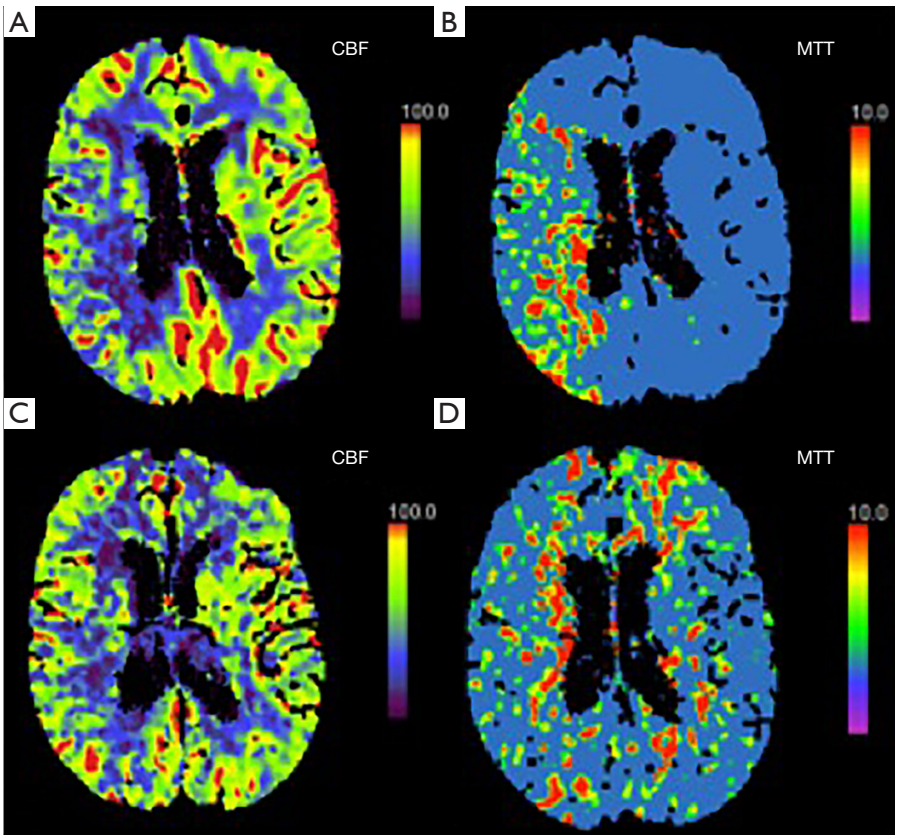

Figure 1 An 87-year-old male with near complete occlusion of his right internal carotid artery (not shown) with evidence of decreased cerebral blood flow (CBF) and increased mean transit time (MTT) throughout the right cerebral hemisphere on pre-operative CT Perfusion (A,B) indicating decreased perfusion. After carotid artery stenting, both the CBF and MTT are more symmetric with the contralateral hemisphere (C,D).

stroke risk markers (41-43).

Some of the methods for measuring cerebrovascular reserve or oxygen extraction fraction require advanced imaging techniques or the use of vasodilatory stimuli that are not always routinely performed. Despite this, many studies have demonstrated that carotid artery stenosis results in downstream hemodynamic alterations, even in asymptomatic patients, and these hemodynamic alterations may increase the risk for future or recurrent stroke.

White matter hyperintensities (WMH)

Leukoaraiosis, or WMH, are frequently encountered "incidentally" on routine brain MR imaging with a prevalence ranging from 11–21% to 94% depending on age (44,45). These brain lesions are most commonly seen as T2 and T2/FLAIR (fluid attenuating inversion recovery) hyperintensities in the periventricular and subcortical white matter. WMH can be measured both quantitatively with various mapping tools and qualitatively using visual rating scales on routine brain MR imaging. Initially thought to be mostly incidental, the presence of white matter hyperintensities has been shown to increase risk of stroke, cognitive decline, dementia, and death (3,4,6). The increased risk of stroke, dementia, and cognitive decline is present in the general population, not just high-risk populations. Multiple mechanistic explanations for the association of WMH and cognitive decline and dementia exist, including the possibility that WMH are a reflection of the association of vascular risk factors or exist concomitantly with ischemic damage leading to dementia. Both increasing age and hypertension are associated with the presence of WMH, but carotid artery atherosclerosis may also play a role in the development of WMH.

The exact association between carotid atherosclerosis and WMH is uncertain with multiple studies demonstrating mixed results. There are a number of studies that demonstrate an association of white matter hyperintensities in the setting of carotid atherosclerosis, even independent of age and hypertension (46,47). Some studies show an association with carotid atherosclerosis and deeper, periventricular WMH, but not with subcortical WMH (48). Increased thickness of carotid intima-media thickness, a surrogate marker for atherosclerosis measured on ultrasound, has also been shown to be associated with increased WMH in multiple asymptomatic cohorts (13). There may be stronger associations with WMH and increased CIMT, than with carotid stenosis. There are inconsistent and mixed results demonstrating hemispheric differences in WMH directly downstream from carotid artery stenosis which makes a direct causative association difficult to establish (49).

There is evidence of increased white matter hyperintensities ipsilateral to "unstable" or high-risk carotid plaque (50,51). The association of increased white matter hyperintensities downstream to unstable carotid plaque were observed regardless of degree of carotid stenosis. These findings may indicate that the thromboembolic plaque activity contributes more heavily to the presence of white matter hyperintensities, rather than hypoperfusion effects. This may be supported by other studies which have shown that the degree of WMH are not associated with CBF in patients with severe carotid stenosis, indicating that WMH may not be seen as a direct result of hypoperfusion (52).

Carotid artery stiffness is an important marker of arterial health and is generally measured on carotid US. Many studies have demonstrated an association between carotid artery stiffness and increased burden of WMH. The presence of carotid artery stiffness on ultrasound has been shown to accurately predict WMH 20 years later (53). Additional studies have shown that larger carotid artery diameters or other findings of extracranial carotid artery remodeling are also associated with the burden of WMH (54).

There is evidence that there is damage to neuronal integrity downstream to carotid artery disease, even before white matter hyperintensities are evident. In asymptomatic patients, there is evidence of microstructural damage and decreased neuronal integrity downstream from carotid artery disease (55). This is evident on sensitive diffusion tensor imaging studies which demonstrate lower fractional anisotropy and higher mean diffusivity values ipsilateral to carotid artery atherosclerosis. These changes in fractional anisotropy and mean diffusivity are indicative of microstructural neuronal damage and have been shown to be associated with cognitive dysfunction and can even be detected in normal-appearing white matter (56), suggesting that neuronal injury may occur before any visible findings on standard MR imaging. Additional studies have shown that larger plaque calcification volume is also associated with worse microstructural integrity measured on diffusion tensor imaging (57).

WMH are frequently noted on routine brain MR imaging and are strongly associated with increased risk of stroke, cognitive decline, and even death. The development of WMH is likely multifactorial with both age and hypertension being established risk factors. There is some evidence, however, that carotid artery disease may also play a role in the development of WMH, given that carotid artery atherosclerosis as measured by CIMT and carotid plaque features and are associated with increased WMH. This association seems to be unrelated to the degree of carotid stenosis, suggesting a negligible role for hypoperfusion in the development of WMH.

Silent brain infarctions

Distinct from WMH, silent brain infarctions (SBIs) are also visualized "incidentally" on routine brain MR imaging. They are defined as infarctions identified with MR imaging which did not present as clinically overt symptoms or signs and were not previously diagnosed as a transient ischemic attack or stroke. While these infarctions, by definition, did not have clinically obvious stroke-like symptoms, they may still be associated with more subtle deficits, both physically and cognitively. For this reason, many are steering away from the calling them "silent" as they can result in functional or cognitive changes, with the term "covert" brain infarcts now increasingly being used (58). Similar to WMH, SBIs are commonly detected on routine MR imaging and are seen in about 20% of healthy elderly people and up to 50% of patients with more risk factors (59). SBIs are important to recognize and report on because they more than double the risk of subsequent stroke and dementia (6,60,61), increase perioperative and long-term stroke risk and mortality in patients undergoing carotid endarterectomy (62), and are strongly associated with cognitive impairment (5,63,64).

Unfortunately, there is no universal definition of imaging criteria for SBI. There are two main categories for covert brain infarctions: (I) lacunar cavitary infarctions, which

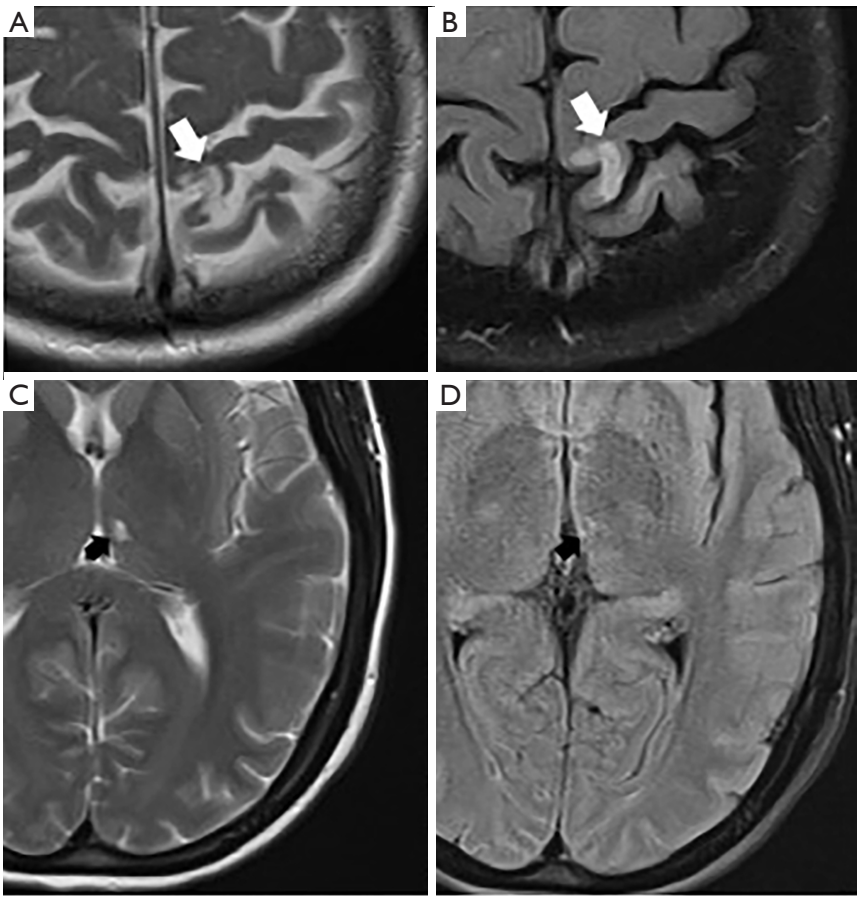

Figure 2 Silent brain infarctions. (A,B) A 78-year-old asymptomatic male with left carotid artery stenosis (not pictured) and encephalomalacia and gliosis in the left parietal lobe (white arrow) consistent with cortical infarction; (C,D) a 63-year-old asymptomatic female with chronic lacunar infarction in the left thalamus.

are most strongly associated with hypertensive small vessel disease and (II) cortical infarctions which may have the same pathophysiology as overt infarctions (*Figure 2*). While there is some variability in the definition of the SBIs, the lacunar subtype of SBIs is most common and are generally defined as a focus in the deep gray or white matter which follows CSF signal on all pulse sequences with a gliotic T2-FLAIR hyperintense rim (65,66). These can be confused with dilated Virchow-Robin spaces which are similarly of CSF signal intensity on all pulse sequences, but do not have a T2-FLAIR hyperintense rim. The cortical subtype of SBIs can occur in any non-eloquent regions of the cerebral cortex. Furthermore, SBIs can also be seen in the cerebellum and brainstem.

There are a number of studies demonstrating the strong association between carotid artery atherosclerosis and the presence of SBIs, in both symptomatic and asymptomatic cohorts (47,61,67-71). A study of asymptomatic patients with carotid artery atherosclerosis found a higher prevalence of SBIs downstream from ICA disease compared to the contralateral side (72). There was a significant difference in cortical SBIs between hemispheres. The lacunar subtype, however, did not show a significant difference between sides. Other preliminary data similarly demonstrated those with asymptomatic carotid stenosis had a greater proportion of cortical SBIs (73). Additionally, there is evidence of an association of SBIs with high-risk plaque features, likely secondary to increased likelihood of emboli (61,74,75). Similar to WMH, increasing carotid lumen diameter and increased carotid stiffness is also found to be associated with increasing prevalence of lacunar infarcts (70).

SBIs likely arise from a variety of potentially independent mechanisms. One major potential cause of SBIs is small vessel vasculopathy, which is supported by the fact that

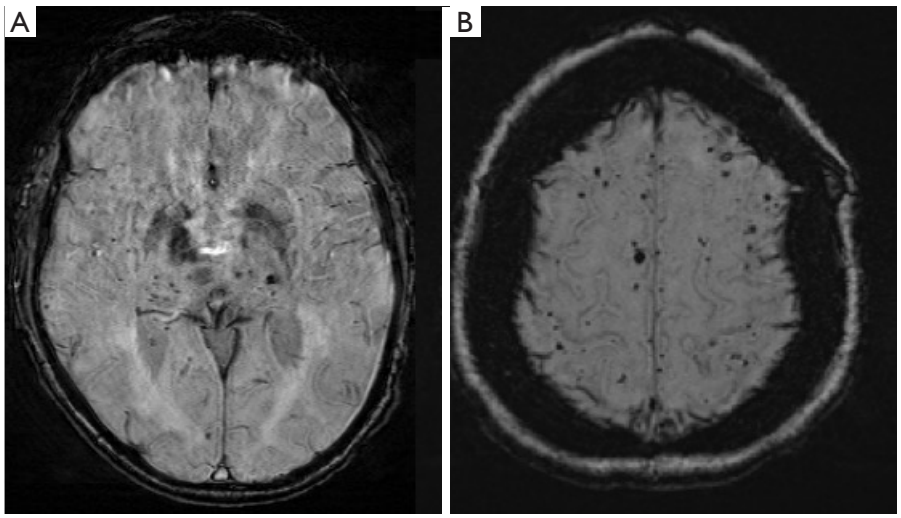

Figure 3 Cerebral microbleeds. (A) A 74-year-old male with multiple foci of susceptibility hypointensity predominantly in the bilateral thalami; (B) a 69-year-old male with multiple foci of susceptibility hyperintensity in a peripheral, lobar pattern, more commonly associated with cerebral amyloid angiopathy.

most SBIs occur in deep gray and white matter where there are smaller vessels and that SBIs are closely associated with leukoaraiosis. There is also evidence that SBIs can be caused by embolic phenomenon and hypoperfusion, both of which can be seen in the setting of carotid artery disease (76-79). Since the association between carotid artery disease and stroke is very well-established, the association between carotid artery disease and certain types of SBIs would also necessarily be strong, given that many of these infarctions have a similar pathophysiology.

Cerebral microbleeds (CMBs)

CMBs are another frequently encountered incidental finding on routine brain imaging. They are small hypointense foci on T2*-weighted gradient echo and susceptibility images on MR. On histopathology, these foci represent small hemosiderin deposits from microvascular leakage. Similar to other previously discussed incidental findings on MR, CMBs are associated with increased risk of ischemic infarctions, intracerebral hemorrhage, cognitive impairment, and dementia (80-84). CMBs are generally asymptomatic and indicate the presence of hemorrhage-prone cerebral small vessel disease. They are most commonly seen in older individuals with an increasing prevalence as patients age, from around 6.5% at age 45 to 50 to 35.7% at age 80 (85). They most commonly are thought to be secondary to hypertension and cerebral amyloid angiopathy. CMBs in the deep or infratentorial regions are generally associated with hypertensive angiopathy while lobar and more peripheral CMBs are more closely associated with underlying cerebral amyloid angiopathy (*Figure 3*). Although hypertension, advancing age, and amyloid angiopathy are well-established risk factors for CMBs, other processes may also be associated with the development of CMBs, including carotid atherosclerosis.

Many studies have identified a link between carotid atherosclerosis and the presence of CMBs. In almost all studies, carotid atherosclerosis was more strongly associated with deep and infratentorial CMBs, as opposed to lobar CMBs which are more commonly associated with cerebral amyloid angiopathy. There have been several studies indicating an association between carotid atherosclerosis, indicated by carotid intima-media thickness and the presence of deep CMBs (86,87). The presence of carotid stenosis ≥25% is associated with the presence of both overall CMBs and at deep and mixed locations (12). Additional studies have shown an association between the presence of carotid artery plaque and CMBs. For example, calcification in the ICA was found to be an independent risk factor for deep CMBs (88). In addition, some studies have shown that there is an association between higher-risk fatty carotid plaques and CMBs (89,90). Furthermore, multiple studies have shown that increased carotid artery stiffness, which is also associated with hypertension, may contribute to the development of CMBs, especially in the deep location (91).

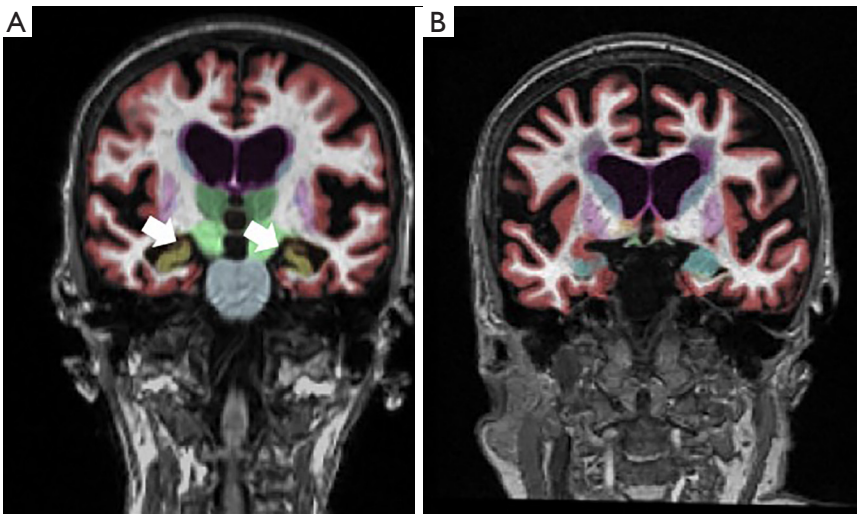

Figure 4 Cerebral volume loss. (A) A 73-year-old female with predominant hippocampal volume loss (arrows); (B) a 77-year-old female with diffuse cerebral volume loss.

These studies suggest CMBs are likely multifactorial and can be present in asymptomatic patients with carotid artery disease.

Brain volume

Decreased cerebral volume and atrophy is also frequently visualized on routine MR imaging (*Figure 4*). This finding is nonspecific and is associated with normal aging (92), dementia including Alzheimer's disease (93), cerebrovascular disease including stroke (94), cardiovascular disease including myocardial infarction (95), and other neurodegenerative disorders (96). The presence of brain atrophy is strongly associated with cognitive impairment (97). Carotid atherosclerosis has also been associated with decreased cerebral volume and brain atrophy, with support from multiple cross-sectional studies. The mechanism underpinning the association between carotid atherosclerosis and decreased cerebral volumes has not been definitely established, though arterial stiffness from carotid atherosclerosis is thought to lead to relative cerebral hypoperfusion and then brain atrophy (98,99). Many studies have shown that both increased CIMT and carotid stenosis are associated with decreased relative total brain and cortical gray matter volume (13,100,101). Increased CIMT is also associated with increased progression of total brain and gray matter volume (102). Furthermore, severe or bilateral carotid stenosis has also been shown to be related to progression of global, cortical, and subcortical atrophy (100). Additional studies suggest the degree of carotid plaque burden may also be associated with cerebral atrophy (103). Furthermore, higher risk carotid plaque characteristics, including ulceration or surface irregularity or heterogeneous echotexture on ultrasound, were also associated with brain atrophy, even after adjustment for age and other cerebrovascular risk factors (67). In addition, larger volume of overall plaque calcification is also associated with decreased brain volume (57).

In addition to overall decreased brain volume and decreased cortical gray matter volume, some studies have also shown an association of carotid atherosclerosis to decreased hippocampal volumes (104). Lower hippocampal volumes are also independently associated with cognitive impairment and dementia.

Conclusions

In addition to the ischemic stroke, carotid artery disease is associated with many downstream markers of cerebrovascular ischemia that can be evaluated on both routine and advanced imaging. Most of these imaging findings are not clinically obvious and can be considered "silent", though there is increasing evidence of their long-term negative impact on patient health outcomes. These imaging findings may be powerful tools in risk stratifying patients with carotid artery atherosclerosis. Using MR or CT perfusion or other nuclear medicine studies to evaluate cerebrovascular reserve or oxygen extraction fraction may

be a helpful tool to identify those who may be more likely to benefit from carotid endarterectomy. The presence of other findings on brain MR, including white matter hyperintensities, silent brain infarctions, and cerebral microbleeds, may influence medical management of risk factors for stroke. Future research efforts are warranted to standardize definitions and validate the use of these neuroimaging findings as potentially powerful biomarkers of brain health in patients with carotid disease.

Acknowledgments

Funding: AG is in part supported by National Institutes of Health grants (R01HL144541 and R21HL145427).

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Dr. Kosmas I. Paraskevas) for the series "Carotid Artery Stenosis and Stroke: Prevention and Treatment Part I" published in *Annals of Translational Medicine*. The article was sent for external peer review organized by the Guest Editor and the editorial office.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-1939). The series "Carotid Artery Stenosis and Stroke: Prevention and Treatment Part I" was commissioned by the editorial office without any funding or sponsorship. HB reports grants from Association of University Radiologists-General Electric Radiology Research Fellowship, during the conduct of the study. AG reports non-financial support from GE Healthcare and non-financial support from Siemens Medical Solutions USA, Inc., outside the submitted work. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Baradaran H, Gupta A. Brain imaging biomarkers of carotid artery disease. Ann Transl Med 2020;8(19):1277. doi: 10.21037/atm-20-1939

