Chapter 7

# Extracranial Carotid Atherosclerosis in the Patients with Transient Ischemic Attack

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**Abstract**

Management of transient ischemic attack (TIA) is important because potentially fatal ischemic strokes can be prevented. Detection of extracranial carotid atherosclerosis in these patients is beneficial because medical therapy can be given, and in certain cases, surgery can be performed. In a Chinese study conducted on the patients with TIA, only 19% of them had extracranial carotid atherosclerosis. Another study was conducted to compare the location and the severity of atherosclerotic lesions between Americans and the Japanese who presented with carotid system TIA. This study showed that 85% of the American patients had extracranial carotid stenosis (stenosis ≥50%). However, only 16.7% of the Japanese patients had similar lesions.

**Keywords:** transient ischemic attack, extracranial, carotid, atherosclerosis, stroke

## 1. Introduction

In the patients with transient ischemic attack (TIA), ischemic strokes often occur early after the first presenting clinical features especially in the first 7 days [1–4]. Management of TIA is important because potentially fatal ischemic strokes can be prevented [5]. It is important to identify the highest risk patients urgently so that the necessary management can be instituted for appropriate early treatments [6, 7].

Neuroimaging is beneficial to stratify the risk of recurrent stroke [8]. The modalities useful for imaging of the extracranial carotid vessels are ultrasound carotid Doppler with/without

enhancement, computed tomography angiography (CTA), magnetic resonance angiography (MRA), and positron emission tomography (PET)/CT [8–14].

With improvements in vascular imaging techniques, it is now possible to risk stratify the patients on the degree of carotid artery stenosis and also on the vulnerability of the plaque to rupture [13]. The risk stratifications are based on the presence of imaging features such as intraplaque hemorrhage (IPH), plaque ulceration, plaque neovascularity, fibrous cap thickness, and presence of a lipid-rich necrotic core (LRNC) [13].

The risk of early recurrent stroke in the patients with TIA is 9.5–20% at 90 days [2, 15, 16].

The risk of early recurrent stroke is highest in patients with large artery atherosclerosis, which consists of extracranial carotid atherosclerosis and intracranial stenosis [9]. Therefore, it is important for urgent ultrasound carotid Doppler and transcranial Doppler (TCD) to be performed in these high-risk patients [9].

The carotid arteries are elastic and are predilection sites for atherosclerosis [17, 18]. Carotid intima media thickening is an indicator for subclinical atherosclerosis, and this frequently occurs earlier than atherosclerosis in coronary arteries and intracranial arteries [17, 18].

The patients who developed a hemispheric TIA due to internal carotid artery (ICA) disease had the greatest risk of ischemic stroke in the first few days after the TIA [9]. Carotid stenosis is associated with recurrent strokes [9, 19]. In the TIA patients, carotid stenosis predicted 90-day stroke [19]. Carotid stenosis is significantly associated with stroke in the short term, and also in the long term for up to 3 years [1].

In a Chinese study conducted on the patients with TIA, only 19% of them had extracranial carotid atherosclerosis [20]. Another study was conducted to compare the location and the severity of atherosclerotic lesions between Americans and the Japanese who presented with carotid system TIA [21]. This study showed that 85% of the American patients had extracranial carotid stenosis (stenosis ≥50%) [21]. However, only 16.7% of the Japanese patients had similar lesions [21]. In another study, the African-Americans had slightly more extracranial carotid atherosclerosis compared to the Caucasians [22].

In a multicenter study on the patients with TIA or minor stroke, 15.5% of the patients (28 out of 85) had at least one stenosis of ≥50% or occlusion [23]. In a recent study, 6.3% of the TIA patients had extracranial carotid artery disease [5]. In that study, 10 (35.7%) patients had moderate stenosis (50–69% stenosis), 8 (28.6%) patients had severe stenosis (70–99% stenosis), and 10 (35.7%) had total occlusion [4]. Five (17.9%) patients had recurrent TIAs before admission [5]. No patient had ischemic stroke within 90 days of TIA onset [5].

In another prospective study on the patients with TIA and minor stroke, extracranial carotid artery occlusion or stenosis ≥50% was found in 9.4% of the patients [8]. In a Japanese study, 21.8% of patients had carotid stenosis [1]. In a study conducted in Ireland, 23.8% of the TIA patients had unilateral carotid stenosis (40.4%, with 50–69% stenosis, 59.6% with ≥70% stenosis or occlusion) [19].

In the study by Coutts et al., 19% of the patients with TIA and minor stroke who developed recurrent stroke had extracranial carotid stenosis ≥50% or occlusion [8]. In comparison, only 9% of the patients with TIA and minor stroke who developed recurrent stroke had similar lesions [8].

A TIA event within 7 days before TIA (dual TIA) is a useful predictive factor for short- and long-term stroke [1]. In addition, ischemic stroke risk is elevated with increasing severity of carotid stenosis [19]. The risk of stroke is 5.4% with <50% carotid stenosis and 17.2% with severe carotid stenosis and occlusion at 90 days after TIA [19].

## 2. Diagnostic modalities

The advantages and disadvantages of the various imaging modalities are illustrated in **Table 1**. Ultrasound carotid Doppler is easily available, cheap, and noninvasive [19]. The sensitivity in carotid stenosis >70% is 91–95% [11, 24]. The specificity in severe stenosis of more than 70% is 86–97% [11, 24]. Being operator dependent is one of the limitations of ultrasound carotid Doppler [11]. The peak systolic velocity (PSV) analysis on the insonated tortuous vessel is difficult, and the stenosis in internal carotid artery (ICA) at the distal end also is difficult to be examined [11].

The diagnostic criteria for stenosis according to The Society of Radiologists in Ultrasound Consensus Criteria for Carotid Stenosis are used to classify the degrees of stenosis [25]. Carotid stenosis of at least 50% is defined as peak systolic velocity (PSV) ≥ 125 and end-diastolic velocity (EDV) ≥ 40. Carotid stenosis of at least ≥70% is defined as peak systolic velocity (PSV) ≥ 230 and end-diastolic velocity (EDV) ≥ 100 [25].

Contrast-enhanced ultrasound is a novel, noninvasive, and cost-effective technique to assess plaque morphology and characteristics [13, 14]. Contrast-enhanced ultrasound assists with the identification of several surrogate markers of vulnerable carotid plaques [14]. The use of ultrasound microbubbles allows a reliable detection of microulcerations [14]. As microbubbles are intravascular tracers, the detection of individual microbubbles inside the plaque signifies intraplaque neovessels [14]. The limitation is the poor sensitivity and specificity for detection of lipid-rich necrotic core and plaque hemorrhage compared with MRI [13].

An early evaluation of the extracranial vessels with computed tomography (CT) and CT angiography (CTA) predicts recurrent stroke and functional outcome in the patients with TIA [8]. In many hospitals especially in the developing countries, CTA is more readily available than magnetic resonance imaging (MRI) due to the cost factor [8]. The doctors will utilize the modality which is more easily and rapidly available in the hospitals [8].

Multislice helical CT scan machines with CTA are widely available in many hospitals [8]. CTA involves the administration of intravenous contrast media to evaluate the extracranial and intracranial vessels with high spatial resolution [8, 26].

Multirow spiral CTA helps with the evaluation of plaques and stenosis [11, 27, 28]. CTA helps to identify large artery atherosclerosis [10, 29]. CT also enables high-resolution imaging and accurately detects ulceration and calcification [13]. The limitation of CTA is the inadequate detection of the morphology of the plaque and its content [11, 27, 28]. In addition, CT is unable to distinguish between lipid-rich necrotic core and intraplaque hemorrhage accurately [13].

There is a technological advancement in the imaging of extracranial carotid atherosclerotic lesions with high-resolution MRI and MRA [11]. Presently, MRI is the gold standard in the

imaging of carotid plaque [13]. MRI has high resolution and high sensitivity for assessment of intraplaque hemorrhage, ulcerated plaque, and lipid-rich necrotic core [30]. The limitation of MRI is time factor [13].

Careful examination of these lesions with high-resolution bright-blood and black-blood MRI analysis of the extracranial carotid vessels accurately evaluates the contents in the plaques [11]. This is performed using the 3.0-Tesla MRI machine [11, 31, 32]. The advantage is the high spatial resolution [11, 31, 32].

The time-of-flight sequence bright-blood technique demonstrates calcified plaques [11, 33]. Black-blood technique is the MRI technique in which the imaging of vessel wall adjacent to the intravascular space is clearer [11, 33]. The bright-blood and black-blood techniques are highly correlated with the diagnosis of contrast-enhanced MRA in the degree of stenosis [11]. The sensitivity and specificity of using MRI technique to detect stenosis of ≥50% are 88.9 and 100%, respectively [11]. The accuracy of MRI diagnosis of similar degree of stenosis is 97.9% [11].

The fibrous cap is isointense in T1-weighted image (T1WI) and hyperintense in proton density weighted image (PDWI) and T2-weighted image (T2WI) [11]. The lipid core is isointense or hyperintense (mild) in T1WI [11]. It is isointense, hyperintense, or hypointense in PDWI and hypointense in T2WI [11].

Ulcerative plaques are characterized by irregular intravascular space surface in the black-blood sequences [11]. In addition, the black hypointensity band is not observed in three-dimensional time-of-flight MRA [11]. The hypointensity band is not continuous, and the intrusion of hyperintensities into the plaques can be picked up [11].

In a recent study on extracranial carotid atherosclerosis with MRI, visual and quantitative analyses demonstrated that the border between the plaque and vessel lumen was better delineated on three-dimensional (3-D) T1-weighted turbo-spin echo black-blood (TSEBB) MRI than on 3-D T1-turbo field-echo black-blood (TFEBB) MRI [12]. Three-dimensional T1-TSEBB MRI was superior to 3-D T1-TFEBB MRI for delineating carotid plaques [12]. But the high signal plaques were underestimated on 3-D T1-TSEBB MRI [12]. In another recently conducted study, 7.0-Tesla MRI enables adequate evaluation to determine luminal and vessel wall areas [34]. Signal hyperintensity in 7.0-Tesla MRI images was inversely proportional to calcification [34].

Positron emission tomography (PET)/CT is an effective modality to evaluate active inflammation in the plaque [13]. However, PET/CT does not allow for assessment of anatomy, ulceration, intraplaque hemorrhage, and lipid-rich necrotic core [13]. In addition, a combination of [18] F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and MRI are complementary to predict high-risk carotid plaque, such as lipid-rich or hemorrhagic plaque [35]. FDG-PET accurately evaluates the lipid-rich and inflamed plaque [35]. MRI is valuable to identify unstable plaque with a large intraplaque hemorrhage [35].

Digital subtraction angiography (DSA) was the gold standard for the assessment of intracranial and extracranial vasculature before the era for MRI [11, 36]. This investigation method

has numerous limitations [11, 36]. Firstly, DSA is invasive [11, 36]. Secondly, the sensitivity is only 46% and the specificity is 74% [11, 36].

Higher levels of cystatin C are independently associated with symptomatic extracranial internal carotid artery (ICA) stenosis, in patients with noncardioembolic stroke [37]. Cystatin C is a biomarker and it is a protein with low molecular weight of 13 kDa [38]. Cystatin C is a cysteine proteinase inhibitor [38].

Cystatin C is an independent risk factor for cardiovascular events and all-cause death in the elderly patients with a normal estimated glomerular filtration rate (eGFR) [39, 40]. It has been suggested that cystatin C levels are associated with inflammation and atherosclerosis [41].

The association between cystatin C and the risk of cardiovascular events is observed in the patients with asymptomatic carotid atherosclerosis, thus ultrasound carotid Doppler can be ordered to detect the carotid abnormalities early [38] (**Table 1**).

| | **Advantages** | **Disadvantages** |
|---|---|---|
| Conventional ultrasound carotid Doppler [11, 24] | • Easily available<br>• Cheap<br>• Noninvasive | • Operator dependent |
| Contrast-enhanced ultrasound [13, 14] | • Noninvasive<br>• Cost-effective<br>• Detection of microulcerations | • Poor sensitivity and specificity for detection of lipid-rich necrotic core and plaque hemorrhage |
| CT/CTA brain and carotid [8, 13, 26–28] | • More easily and rapidly available in the hospitals due to lower cost<br>• High spatial resolution | • Administration of contrast media, therefore can cause allergy<br>• Inadequate detection of the morphology of the plaque and the content<br>• Cannot distinguish between lipid-rich necrotic core and intraplaque hemorrhage accurately |
| MRI/MRA brain and carotid [11, 13, 30] | • Gold standard in the imaging of carotid plaque<br>• High resolution and high sensitivity to assess intraplaque hemorrhage, ulcerated plaque, and lipid-rich necrotic core | • Time factor<br>• Cost factor |
| PET/CT [13, 18, 35] | • Evaluates active inflammation in the plaque | • Not good in the assessment of anatomy, ulceration, intraplaque hemorrhage, and lipid-rich necrotic core |
| Digital subtraction angiography [11, 36] | • Very accurate | • Invasive<br>• Poor sensitivity<br>• Poor specificity |

**Table 1.** Advantages and disadvantages of the various imaging modalities.

## 3. Therapeutic options

Detection of extracranial carotid atherosclerosis in these patients is beneficial because proper management can be given [32, 42]. The patients with TIA due to extracranial carotid stenosis should be given intensive medical therapy [42]. Intensive medical therapy consists of pharmacological management and lifestyle interventions [42].

The pharmacological management involves antiplatelet therapy and statin use [5, 42]. The antiplatelet therapy which routinely administered is aspirin or clopidogrel [43]. Adequate blood pressure control is necessary with a target blood pressure of less than 140/90 [42]. A reduction in blood pressure to the ideal level slows down the progression of carotid artery stenosis and also reduces the carotid intima media thickness (CIMT) [43]. Identification and treatment of vascular risk factors are important [43].

Lifestyle changes involve Mediterranean-style diet, exercise, and smoking cessation [42, 43]. In addition, lifestyle choices such as unhealthy diet and excessive alcohol intake are modifiable risk factors [43]. The combination of dietary modification, physical exercise, and use of aspirin, statin, and an antihypertensive agent can give a cumulative relative stroke risk reduction of 80% [43]. The antiplatelet therapy and statin use reduce the risk of recurrent stroke in patients with symptomatic extracranial carotid stenosis [5].

## 4. Carotid endarterectomy and carotid artery stenting

In the patients with carotid stenosis of 70–99%, the revascularization procedures such as carotid endarterectomy (CEA) and carotid artery stenting (CAS) may be considered [5, 42]. The patient with a low-grade stenosis but an ulcerated plaque or intraplaque hemorrhage may benefit more from a revascularization procedure than a patient with a stable 70% asymptomatic stenosis with a thick fibrous cap [13].

## 5. Carotid endarterectomy and carotid artery stenting in symptomatic extracranial carotid stenosis

Carotid endarterectomy and carotid artery stenting reduce the risk of recurrent stroke in patients with symptomatic extracranial carotid stenosis [5]. The revascularization procedures reduce the 90-day risk of subsequent ischemic stroke in the patients with severe extracranial carotid artery stenosis [5]. While awaiting the revascularization procedures, a combination of aspirin and clopidogrel in recently symptomatic patients with carotid stenosis can be given [43].

MR plaque imaging is useful in identifying revascularization candidates who are better candidates for carotid endarterectomy than carotid artery stenting [13]. This is because high

intraplaque signal on time-of-flight imaging is associated with vulnerable plaque and in-creased rates of adverse events in patients undergoing stenting but not carotid endarterectomy [13].

In the recent guidelines, carotid endarterectomy is likely the preferred option for the management of asymptomatic carotid stenosis [44, 45]. Carotid artery stenting has higher risk of periprocedural stroke and mortality [44–46]. Carotid endarterectomy is safer in comparison to carotid artery stenting [44, 45]. The risk of periprocedural stroke and mortality after carotid endarterectomy has declined tremendously throughout the years [47].

However, carotid endarterectomy is associated with an increased risk of periprocedural myocardial infarction [44, 45, 48]. To date, the long-term outcomes of these two modalities remain uncertain [44]. In patients with high risk of periprocedural complications, best medical treatment is recommended by the American Heart Association and the Society for Vascular Surgery [32, 44, 49].

## 6. Conclusion

In conclusion, evaluation of extracranial carotid atherosclerosis in the patients with TIA is very important. There are several modalities which can be employed to investigate for extracranial carotid stenosis. Pharmacological and nonpharmacological management can be given to the patients with extracranial carotid atherosclerosis.

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