Chapter 5

Risk Factors in the Patients with Extracranial Carotid Atherosclerosis

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Abstract

There are vascular risk factors known to be associated with stroke. These risk factors have been shown to either directly or indirectly lead to stroke. The risk factors include hypertension (HT), diabetes mellitus (DM), smoking, hyperlipidaemia, ischemic heart disease (IHD) and atrial fibrillation (AF). Studies have shown that carotid atherosclerosis is a cause of stroke. Extracranial carotid atherosclerosis accounts for up to 40% of the ischemic strokes in the Western countries. The latest stroke guidelines recommend the routine use of Ultrasound Carotid Doppler to assess for extracranial carotid artery atherosclerotic diseases (carotid intima media thickness, plaques, carotid stenosis) in these patients. A previous study emphasized the value of carotid ultrasonography in the detection of early extracranial carotid atherosclerosis.

Keywords: extracranial, carotid, atherosclerosis, risk, factors

1. Introduction

Stroke is one of the most common diseases in the world and results in up to 10% of mortality globally [1]. Stroke is the third leading cause of mortality and long-term disability in the United States of America [2].

There are vascular risk factors known to be associated with ischemic strokes [3]. These risk factors have been shown to either directly or indirectly lead to stroke [3]. The risk factors include hypertension (HT), diabetes mellitus (DM), smoking, hyperlipidaemia, ischemic heart disease (IHD) and atrial fibrillation (AF) [3].

Studies have shown that carotid atherosclerosis is a cause of stroke [4]. Annually, about 20–30% of new strokes are due to atherosclerotic carotid artery disease [5]. The latest stroke guidelines recommend the routine use of ultrasound carotid Doppler to assess for extracranial carotid artery atherosclerotic diseases (carotid intima media thickness, plaques, carotid stenosis) in these patients [6].

Ultrasound carotid Doppler is a non-invasive and cost-effective test [7]. Carotid intima media thickness (CIMT) measurements and plaque location are evaluated on gray scale imaging (B-mode) [7]. Flow disturbance and stenosis is assessed on color Doppler [7]. The blood flow velocities are examined on spectral Doppler [7].

A previous study emphasized the value of ultrasound carotid Doppler in the detection of early extracranial carotid atherosclerosis [4]. In the world, an increased CIMT is found in 9.4% of the men and 11.7% of the women [4]. Assessment of CIMT increases with ultrasound carotid Doppler in the subjects without carotid atherosclerosis and free of previous vascular events predicts the occurrence of carotid plaque [8].

The prevalence of carotid plaque is 13.3% in the men and 13.4% in the women in the world [8]. The prevalence of extracranial carotid stenosis is 2.7% in the men and 1.5% in the women globally [8]. Stroke is associated with the plaques containing softer tissue, especially with thin fibrous cap [2].

Hyperlipidaemia is a common risk factor for extracranial atherosclerosis [9]. The risk factor of hyperlipidaemia was one of the two most common risk factors for stroke in Singapore (76.5–86.4%) [3]. Hyperlipidaemia results in an atheroma or a fibrofatty plaque leading to gradual occlusion of the arteries. As the plaques increase in size, they progressively occlude the lumen and compromise the blood flow causing stroke [10]. In the South Korean studies, extracranial atherosclerosis was associated with higher LDL levels [9, 11].

Furthermore, low levels of HDL cholesterol are associated with an increased risk of having echolucent, rupture-prone atherosclerotic plaques [12]. In addition, an increased risk of having an echolucent plaque is independently associated with increasing degree of stenosis [12]. The subjects with echolucent plaques have increased risk of ischemic cerebrovascular events and stroke independent of the degree of stenosis and cardiovascular risk factors [13].

A community-based study in Taiwan showed that hypertension strongly influenced extracranial carotid atherosclerosis and hypertension was the predictor of carotid stenosis ≥50% [14, 15]. The frequencies of hypertension among the stroke patients in the other Asian countries were: 59% in Pakistan [16], 38.3% in Japan [17], and 19–28% in China, Korea and Taiwan [17].

There are several mechanisms of stroke due to hypertension. High blood pressure results in endothelial damage, which leads to thrombi formation [18]. Hypertension is also known to accelerate the atherosclerotic process [18]. Moreover, in the general population, hypertension is a predictor of the occurrence of plaques [8]. Systolic blood pressure is significantly associated with severe extracranial carotid atherosclerosis (plaque, stenosis) [4].

The percentages of ischemic stroke patients with DM were 37% in Pakistan [16] and 30% in South Korea [11]. DM is an important risk factor for extracranial carotid atherosclerosis [14, 19]. DM affects the vascular endothelium and reduces the bioavailability of nitric oxide (NO), which is a major anti-atherosclerotic agent [20–22]. Hyperglycemia inhibits the production of NO by restraining the activation of endothelial NO synthase [23]. In addition, the prevalence of extracranial carotid atherosclerosis is significantly higher in the ketosis-onset DM patients than in the control subjects [24]. The frequency of extracranial carotid atherosclerosis in the ketosis-onset DM patients is similar to the non-ketotic type 2 DM patients [24].

Smoking is also known to be associated with atherosclerosis of the extracranial carotid vessels [14]. The percentage of the patients with smoking history was 25% in Wasay et al.'s study [16]. Smoking leads to damage of cells that line the arteries. In addition, smoking increases the build-up of plaque constituents in the arteries. Moreover, smoking results in thickening and narrowing of the arteries [25].

Smoking history is a determinant of the occurrence of a new carotid plaque in the subjects with no previous carotid atherosclerosis and also free of previous vascular events [8]. In addition, there is a significant association between severe extracranial carotid atherosclerosis and smoking [4]. Furthermore, smoking was found to be associated with carotid plaque and extracranial carotid stenosis in several studies [9, 26, 27]. Cessation of smoking will be helpful in the management of these stroke patients.

IHD and ischemic stroke are vascular diseases [28]. IHD was present in 11.8–20% of the Singapore stroke patients [3]. Moreover, IHD was associated with carotid stenosis in a study [27]. In another study conducted in Japan on consecutive patients who had coronary angiography, 6% of them had extracranial carotid stenosis [29].

AF is known cardiovascular risk factor of stroke [30]. AF can predispose to embolism and stroke [31]. AF is commonly associated with stroke in South Asia, Western Europe, North America and Australia [32]. Increased CIMT and presence of carotid plaque are associated with increased risk of ischemic stroke in the patients with AF [33]. Higher CIMT and the presence of carotid plaque are associated with higher incidence of AF incidence [34].

Age is an important risk factor for extracranial carotid atherosclerosis, especially in the Chinese and South Koreans [9, 11, 14, 19, 35]. These patients tend to be older in age [9, 11, 19, 35]. Age is a significant predictor of the occurrence of a new carotid plaque in the general population [8]. The incremental probability of the occurrence of plaque is higher in the subject's midlife [8]. In the subjects aged ≥40 years old, the severity of carotid atherosclerosis (plaques, stenosis) was significantly associated with age [4]. Moreover, the frequency of extracranial carotid atherosclerosis significantly increases with age in the DM patients (ketosis-onset and non-ketotic DM) [24].

Male gender is also risk factor for extracranial atherosclerosis [9, 19]. 14.8% of the patients with extracranial atherosclerosis, had family history of stroke [9]. In a Chinese study, 48.4% of the healthy population with extracranial carotid atherosclerosis had obesity [19].

Elevated CIMT is associated with an increased risk of stroke [20]. Plaque rupture with subsequent embolism can lead to stroke [20]. The presence of plaque is associated with an increased risk morbidity and mortality secondary to stroke [28].

One population study showed the relationship between extracranial carotid atherosclerotic lesions with the classic risk factors such hypertension, hyperlipidaemia and smoking [28].

An European Rotterdam Elderly Study showed that hypertension, smoking and reduced serum HDL were associated with carotid artery stenosis [36]. In that study, factor VIIc and factor VIIIc (hemostatic factor) activity was higher in the patients with extracranial carotid disease [36].

Altogether, the number of classic risk factors among the patients with extracranial atherosclerosis was 1.67 in a South Korean study [11]. The number of traditional risk factors in the patients with severe extracranial atherosclerosis was almost similar (1.68) [11].

CIMT is a marker of subclinical atherosclerosis and hypertension has been known to be risk factor of atherosclerosis [28]. Therefore, proper monitoring of CIMT and treatment can potentially be helpful to these patients to prevent further progression to plaques and stenosis. In a previous study, 18.2% of the patients with extracranial atherosclerosis had history of previous stroke [11]. Among the patients with severe extracranial atherosclerosis, 21.6% of them had history of previous stroke [11].

Furthermore, a study by Amarenco et al. showed that there was a higher prevalence of coronary plaques, with concomitant carotid plaques, in patients with non-fatal ischemic stroke with no known IHD [37]. In a study done among Chinese patients, 7.8% of the patients with paroxysmal AF had a combination of extracranial carotid stenosis and IHD [30].

The miR-146a rs2910164 polymorphism may be associated with carotid vulnerable plaque risk in the Chinese patients with type 2 DM, particularly in older patients and women [38]. This polymorphism may be associated with carotid vulnerable plaque risk in the patients with DM duration of >10 years and the patients with hypertension [38].

In addition, the metabolically abnormal but normal weight subjects have increased CIMT compared to the metabolically healthy but obese subjects and metabolically healthy normal weight subjects [39]. The patients with extracranial carotid atherosclerosis are more likely to have contralateral extracranial carotid atherosclerosis [26].

In terms of ethnic variation, the South Asians have the higher prevalence of extracranial carotid atherosclerosis compared to the Europeans and Chinese [20]. The South Asians have an increased frequency of impaired glucose tolerance, hypercholesterolemia (higher total and LDL cholesterol), hypertriglyceridemia and lower HDL cholesterol [20]. In addition, the South Asians have higher concentrations of fibrinogen, homocysteine, lipoprotein (a), and plasminogen activator inhibitor-1 [20].

The Chinese have lower rates of cardiovascular disease than the Europeans [40]. Furthermore, the Chinese have a more favorable risk factor profile except for impaired glucose tolerance [40]. The Europeans are more likely to be current or former smokers [20]. The Caucasians with severe extracranial carotid stenosis are more obese than those without such stenosis, unlike the Japanese [41].

In conclusion, proper identification and optimization of the risk factors in the patients with extracranial carotid atherosclerosis in important. This will help to prevent or slow down the progression of the extracranial carotid atherosclerosis. By preventing the development of carotid stenosis, the occurrence of ischemic stroke can be minimized (**Figure 1** and **Table 1**).

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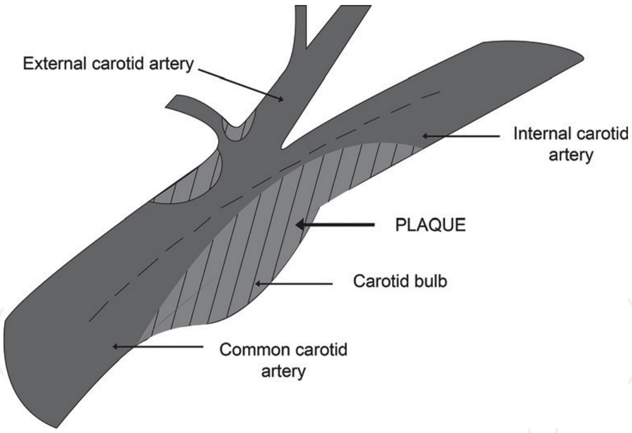

Figure 1. Diagram showing plaques at the carotid bulb extending to the internal carotid artery [2].

1. Hypertension
2. Diabetes mellitus
3. Hyperlipidaemia
4. Smoking
5. Ischemic heart disease
6. Atrial fibrillation
7. Advancing age
8. Male gender
9. miR-146a rs2910164 polymorphism
10. Metabolically abnormal but normal weight

Table 1. Risk factors of extracranial carotid atherosclerosis [9, 14, 18, 19, 28, 30, 38, 39].

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