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Risk Factors of Ischemic Stroke: A Literature Review

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ABSTRACT

A stroke or a cerebrovascular accident can be defined into 2 major types, ischemic and hemorrhagic. Ischemic stroke is the more prevalent type of stroke. Identifying and understanding the risk factors of ischemic stroke is imperative. Nonmodifiable risk factors include age, sex, and previous stroke history. Nonmodifiable risk factors play a role in worsening pre-existing modifiable risk factors, the absence or presence of endogenous estrogen, and endothelial dysfunction. Modifiable risk factors include hypertension, diabetes mellitus, dyslipidemia, and smoking. Modifiable risk factors increase the risk of a stroke by endothelial dysfunction, emboli and/or thrombus formation, chronic inflammation, and atherosclerosis. This study will give a more in-depth view of how these risk factors influence the possibility of ischemic stroke.

Keywords: stroke; risk factors; hypertension; diabetes mellitus; smoking; age; dyslipidemia.

INTRODUCTION

A stroke can be defined as a neurological injury in the central nervous system attributed to vascular issues. Stroke can cause disabilities in adults and is known to be a major contributor od DALYs (disability-adjusted life year). In 2019, there were 77 million cases of ischemic stroke worldwide. The high prevalence of ischemic stroke can be attributed to rising risk factors [1,2,3]. Stroke is divided into two types, ischemic and hemorrhagic with ischemic being the more prevalent type contributing to a staggering proportion of strokes worldwide [4,5,6].

ISCHEMIC STROKE

Definition of Ischemic Stroke

Ischemic stroke occurs when there is insufficient blood supply to the brain. This insufficiency is caused by an obstruction by thrombosis or emboli. In the case of thrombosis, the blood in the vessels going to the brain is obstructed by a dysfunction within the vessel itself. This thrombosis usually follows an atherosclerotic disease, arterial dissection, fibromuscular dysplasia, or is caused by an inflammatory condition. On the other hand, if it is caused by an emboly, it means that there is debris from other parts of the body blocking the blood flow to the brain [7]. In addition, in the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, ischemic stroke is divided into five subtypes namely, large artery atherosclerosis (LAA), cardioembolism (CE), small vessel occlusion (SVO), stroke of other determined etiology, and stroke of undetermined etiology [8].

Pathophysiology

As mentioned above ischemic strokes happen due to a thrombotic event or an embolic event. In a thrombotic event, blood flow decreases due to the narrowing of the blood vessels such as atherosclerosis. Atherosclerosis is the build-up of plaque inside the artery. On the contrary, embolic events happen when a clot an air bubble, or any foreign body blocks an artery. Both of these events, cause a decrease in blood supply thus causing a decrease in oxygen supply as well. This will in time cause necrosis. Due to this nature, medical professionals can determine which part of the brain is affected by the stroke. This is if there is/are pre-determined syndromes in the patient [7,9,10,11].

The most common artery involved in stroke is the middle cerebral artery (MCA). The MCA supplies blood to the lateral surface of the brain, a portion of the basal ganglia, and the internal capsule through segments M1, M2, M3, and M4. M1 and M2 play a pivotal role in body functions, M1 supplies the basal ganglia that is involved in motor control, motor learning, executive functions, and emotions, while

M2 supplies the insula, superior temporal lobe, parietal lobe, and inferolateral frontal lobe. If the affected vessel is the MCA, then the clinical presentation may show facial paralysis, contralateral hemiparesis, and sensory loss in the face and upper extremities [7].

Moving on, the anterior cerebral artery (ACA) is also often affected by ischemic stroke. The ACA supplies blood to the frontal, prefrontal, primary motor, primary sensory, and supplemental motor cortices. Within the supplemental motor area is the Broca area which is responsible for speech. In addition to that, the ACA is also involved in the medial cerebral cortex which is involved in motor and sensory functions in the lower extremity. Consequently, if the ACA is the affected vessel, then the patient may be present with contralateral sensory and motor deficits in the lower extremities and may have difficulty responding with speech [7].

Whereas if the affected vessel is the posterior cerebral artery (PCA), the patient may show signs of hypersomnolence, cognitive deficits, ocular findings, hypoesthesia, and ataxia. This is because the PCA supplies blood to the occipital lobe, the temporal lobe, the thalamus, and the internal capsule. The occipital lobe is involved in vision while the thalamus is responsible for relaying information between the ascending and descending neurons [7].

The vertebral arteries and the basilar arteries supply blood to the vertebrobasilar region of the brain, the cerebellum, and the brainstem. If these arteries are affected then the clinical presentation includes amongst others, ataxia, vertigo, headache, vomiting, oropharyngeal dysfunction, visual-fields deficits, and abnormal oculomotor findings. If the cerebellum is affected then patients may be present with ataxia, nausea, vomiting, headache, dysarthria, and vertigo [7].

NONMODIFIABLE RISK FACTOR

Age

Age is one of the nonmodifiable risk factors for ischemic stroke. Around three-quarters of all strokes occur in patients aged ≥65 years. Rates of stroke doubles every decade after the age of 55. Aging causes structural and functional changes to the cerebral circulation. This is especially so in cerebral microcirculation. Microcirculatory changes can be associated with endothelial dysfunction, impaired cerebral autoregulation, and impaired neurovascular coupling. In which, endothelial dysfunction induces neuroinflammation, impaired cerebral autoregulation may cause microvascular injury, and impaired neurovascular coupling induces a decrease in cortical function [12,13].

With age, the prevalence of certain risk factors for ischemic stroke increases such as diabetes and hypertension. In addition, multi-morbidity (a person having two or more chronic conditions) is also highly prevalent in older people. It is estimated that 89% of those aged ≥65 years have multi-morbidity, subsequently, those with multi-morbidity are also prevalent in stroke incidents. Based on the incidence of stroke in the age group alone, age can be classified as a nonmodifiable risk factor. However, it should be known that age as a risk factor is very variable, other factors such as sex and lifestyle may modulate age as a risk factor to elevate the risk for ischemic stroke [12, 14].

Sex

Sex as a risk factor for ischemic stroke is dependent on age as mentioned above. It is found that women are at more risk of ischemic stroke than men at a young age. This is likely due to pregnancy, post-partum state, and the use of hormonal contraceptives. Oral contraceptive use has been shown to increase the risk of stroke in women. The Greater Cincinnati-Northern Kentucky Stroke Study (GCNKSS) found that women under the age of 34 years old had a higher incidence of stroke than men. Another study in Sweden found that the incidence of stroke is 60% lower in women aged 55-64 years old than men but found a 50% higher incidence in women aged 75 years old. Overall, it is found that stroke happens more often in women [14, 15, 16].

Estrogen has been found to play a role in preventing stroke. Premenopausal women have hormonal protection from estrogen as estrogen promotes dilation and blood flow whereas testosterone does the opposite effect. Due to this, ischemia is less likely to happen thus creating less risk for women. However, as mentioned above oral contraceptives actually can increase the risk for ischemia up to three times. In the United States, 64.9% of women, or about 46.9 million women aged 15-49 use contraception. Where 12.6% of them use oral contraceptives. This might explain why the incidence of stroke is higher in younger women [16,17].

Previous Stroke History

Patients who have experienced an ischemic stroke are at high risk of experiencing a recurrent stroke. Due to improvements in stroke management and treatment, the mortality of ischemic stroke decreases. However, recurrent stroke is still frequent. Currently, around 80-85% of ischemic stroke patients survive but 15-30% experience a recurrent stroke within the first 2 years. Recurrent strokes cause a much more detrimental neurological impairment and have higher mortality. The chances of a recurrent stroke happening are very dependent on the etiology of the first stroke. It is found that large artery atherosclerosis (LAA) and cardioembolic (CE) stroke subtypes have the highest recurrence rate. This may be associated with the fact that both subtypes cause extensive vascular deficits and ischemia due to occlusion in large cerebral arteries or by an embolus [18,19].

However, Zhuo et al. [19] believe that accurate risk assessment is vital in predicting stroke recurrence. Hypertension is seen to be associated with stroke recurrence. Diabetes Mellitus (DM) has also been identified as a risk factor for recurrent stroke. Smoking, as well as age, are independent risks for stroke recurrence [18,19].

MODIFIABLE RISK FACTORS

Hypertension

Hypertension, also known as high blood pressure, is when a person has a consistent raised pressure within their blood vessels. The human heart pumps out blood to the vessels, this causes a force for the blood to exit the heart and into other organs of the body. Naturally, the blood pushes in all directions and against the blood vessels, this is called blood pressure [20]. According to AHA in Flack and Adekola [21], blood pressure is classified into normal blood pressure, elevated blood pressure, grade 1 hypertension, and grade 2 hypertension. The following are the blood pressure categories:

- Normal blood pressure, systolic <120 mmHg and diastolic <80 mmHg
- Elevated blood pressure, systolic 120-129 mmHg and diastolic <80 mmHg
- Stage 1 hypertension, systolic 130-139 mmHg and diastolic 80-89 mmHg
- Stage 2 hypertension, systolic ≥140 mmHg and diastolic ≥90 mmHg

Hypertension is notably one of the most prevalent risk factors for stroke. It is proven to have a strong relationship to stroke. Furthermore, even populations where they are not defined as hypertension but have elevated blood pressure are at a higher risk of stroke. According to INTERSTROKE, 54% of the stroke population had been attributed to hypertension. In this case, hypertension was defined by a history of hypertension as well as blood pressure measurements ≥ 160/90 mmHg [15].

Hypertension is a prominent risk factor due to the intracerebral vascular changes that it causes. The high intraluminal pressure in acute hypertension increases the permeability of the blood-brain barrier (BBB). Hypertension causes impairment to the endothelium and alters endothelium-blood cell interaction that influences vascular tone and/or permeability. This is due to the overproduction of nitric oxide (NO) caused by endothelial dysfunction. The increased permeability of cerebral vessels magnifies the risk of brain edema. Additionally, in ischemic stroke, the altered endothelium-blood cell interaction increases the possibility of local thrombi formation. Chronic hypertension is known to cause fibrinoid necrosis that opens the possibility for lacunar infarcts due to severe stenosis or occlusion [22].

In addition, hypertension speeds up arteriosclerosis. It initially starts in the larger extracerebral arteries, most commonly in the carotid bifurcation. This progresses distally toward the circle of Willis and will gradually reach the small intracerebral arteries. Furthermore, carotid stenosis is also capable of compromising cerebral circulation, and emboli from plaques in both the carotid and vertebral arteries are able to cause ischemic stroke [22]. Hypertension can cause changes in the structure and composition of the cerebrovascular wall that may promote the possibility of atherosclerotic plaques. These plaques may lead to occlusions and ischemia.

Furthermore, hypertension is also known to induce lipohyalinosis in vessels that supply the white matter that can cause infarcts [23].

As mentioned above, hypertension increases intraluminal pressure and prolonged increased intraluminal pressure causes hypertrophy and remodeling of smooth muscles in systemic and cerebral arteries. This is done to reduce the stress of the vessel walls in an attempt to protect the microvessels. This hypertrophy causes the vessel lumen to narrow leading to vascular stiffness. In this process, there are a number of factors that influence the hypertrophy of cerebral arteries, particularly Angiotensin II (Ang II). Angiotensin II plays a significant role in cerebrovascular remodeling alongside reactive oxygen species (ROS). ROS advances the proliferation of smooth muscles and induces the remodeling of extracellular matrix through activation of matrix metalloprotease. Extracellular matrix proteins along with integrin αvβ3, emilin-1, and elastin-1 are involved in hypertrophy, remodeling, and stiffening of blood vessels [22,23].

When ROS exceeds the capacity of the antioxidant defense system, oxidative stress happens. Constant oxidative stress can reduce antioxidant molecules, inactivate antioxidant enzymes, and impair the antioxidant defense system. Oxidative stress is known to cause stress within cerebral blood vessels which in time can lead to stroke. ROS is involved in cerebrovascular dysfunction induced by Ang II by activation of NADPH oxidase. The increased NO and radical superoxide can produce peroxynitrate that can cause DNA damage and lipid peroxidation [23].

Inflammation has shown to be a biomarker capable of predicting ischemic stroke, e.g., C-reactive protein, interleukin-6 (IL-6), leukocyte elastase, lipoprotein (a), intercellular adhesion molecule-1 (ICAM-1), and E-selectin. Blockage or reduction of inflammation has been seen to alleviate hypertension. Moreover, hypertension-induced oxidative stress promotes inflammatory reactions in cerebral blood vessels. Also, inflammation is able to cause oxidative stress, further increasing the risk of ischemic stroke [23].

Another important mechanism in controlling blood pressure regulation is arterial baroreflex. Baroreflex sensitivity has been found to be an important determinant in several cardiovascular diseases. Arterial baroreflex function is involved in the pathogenesis and prognosis of atherosclerosis. The insensitivity of baroreflex is caused by changes in vascular tone and altered activity in the brainstem in a change of reflex. Reduced baroreflex sensitivity can result in arterial stiffness. To boot, baroreflex impairment has also been present several times in both acute ischemic and hemorrhagic stroke [23].

Dyslipidemia

The imbalance of lipids, including triglycerides, high-density lipoprotein (HDL), low-density lipoprotein cholesterol (LDL-C), and cholesterol, is known as dyslipidemia.

This disorder can be hereditary, caused by dietary composition, or result from tobacco use [24]. Cholesterol in the blood has a significant role in the development of cardiovascular diseases [25].

Dyslipidemia as a risk factor for stroke has been confirmed by the 5-year Stroke Prevention by Aggressive Reduction in Cholesterol Level (SPARCL) study. The SPARCL study focused on targeting blood lipids in preventing stroke recurrence and gave sufficient evidence of lipid-lowering therapy in treating ischemic stroke [26].

Dyslipidemia can cause a buildup of lipids in arterial walls that cause atherosclerosis. The narrowing in the lumen caused by plaque, and the buildup of lipids, clog up the blood supply which can cause thrombo-embolism leading to ischemic stroke [27]. In addition, atherosclerosis promotes atherothrombotic and cardioembolic stroke [28].

Furthermore, dyslipidemia causes endothelial damage that can lead to increased blood pressure. Blood lipid levels and hypertension have also been shown to have a relation, suggesting that hypertension may be a product of atherosclerosis caused by hypertension [29].

Diabetes Mellitus

Diabetes mellitus (DM) is a condition where the body is unable to control glucose blood levels. It is classified into several subtypes such as type 1, type 2, maturity-onset diabetes of the young (MODY), glucocorticoid-induced diabetes, and neonatal diabetes. These subtypes are divided by their different pathophysiology, presentation, and management. DM is mainly divided into 2 types which are type 1 and type 2 [30].

Type 1 diabetes mellitus (T1DM) is predominantly present in children or young adults. T1DM happens when the beta cells in the pancreas are destroyed thus unable to secrete insulin. Whereas type 2 diabetes mellitus is predominantly present in adults and seniors. This is because T2DM is caused by an insensitivity towards insulin. Insulin resistance is influenced by a number of things but it usually stems from obesity and aging. As mentioned, prior, T2DM is multifactorial, it is also influenced by genetics and lifestyle. However, T2DM is also known to be more genetically influenced than T1DM [30].

Endothelial dysfunction, like in hypertension, is also a mechanism in which diabetes correlates with stroke. Vascular endothelial function plays a pivotal role in the structure and functions of the vessel wall. Vasodilation utilizes nitric oxide (NO) and when the supply of NO is insufficient, endothelial dysfunction occurs and can promote atherosclerosis. Diabetes is suspected to inactivate NO or desensitize smooth muscle to NO, this impairs NO-mediated vasodilation. Additionally, T2DM patients have stiffer and less elastic arteries compared to people with normal blood glucose levels. Whereas, in T1DM, patients are seen to show early signs of atherosclerosis.

Moreover, patients with diabetes are seen to have an exacerbated inflammatory response, which promotes atherosclerotic plaque. T2DM patients are also known to be more at risk of congestive heart failure. This is influenced by microvascular disease, metabolic derangements, hypertension, interstitial fibrosis, and autonomic dysfunction [31].

Smoking

Smoking cigarettes is known to be a prominent risk factor for stroke. The mechanism by which smoking relates to stroke varies. However, the risk for stroke is increased by 2-4 times more than a non-smoker. The possible linkage between smoking and stroke includes carboxyhemoglobinemia, increased platelet aggregability, increased fibrinogen levels, low HDL levels, and toxic radicals. All of these phenomena increase the progressivity of atherosclerosis. As mentioned, prior, atherosclerosis is a mechanism in most risk factors for stroke. In addition, smoking-induced vasoconstriction causes impairment to fibrinolysis as well as reduced blood flow in the brain [32].

CONCLUSIONS

Ischemic stroke is a condition that happens when the brain does not receive an ample supply of blood and becomes ischemic. This happens because there is a blockage in the arteries that supply blood to the brain. The risk of a blockage increases because of risk factors, nonmodifiable and modifiable. Nonmodifiable risk factors include age, sex, and previous stroke history. Whereas, modifiable risk factors include hypertension, dyslipidemia, diabetes mellitus, and smoking.

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