

Epidemiology and risk factors of cerebrovascular disease

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Abstract:

Background: The cerebrovascular disease represents the second cause of death in the world. Mortality from this pathology is only part of the problem since the subjects who survive it experiences many sequelae that generate disability, affecting activities of daily living and productivity, making it a significant public health problem worldwide.

Contents: In this review, we summarize the current literature on the epidemiology, etiology, and risk factors associated with cerebrovascular disease to understand and promote that stroke can be preventable. This review also explores the evidence from clinical studies in subjects with stroke and its relationship with the different modifiable and non-modifiable risk factors. Finally, it will address how stroke affects motor functioning, an activity closely related to activities of daily living such as personal maintenance tasks, mobility, home management, and productivity, which are necessary to achieve independence in their environment.

Conclusion: Stroke is one of the diseases that causes the highest rates of disability in the world, affecting the social participation of patients and leisure activities, reducing their mobility and negatively impact daily activities. Many factors can increase the risk of having a stroke. Potentially treatable and preventable risk factors for stroke include obesity, physical inactivity, smoking, hypertension, and high cholesterol levels, among others. Therefore, it is required to have healthy lifestyle habits. Diet, exercise, and weight loss can help reduce blood pressure, excess weight, and cardiovascular disease, thereby reducing the incidence of stroke.

Key Word: Stroke, Ictus, Activities of daily living, Risk Factors, Epidemiology

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I. Introduction

Cerebrovascular disease, also called ictus or stroke, is an alteration in the blood vasculature of the central nervous system (CNS), which produces neuronal death due to an imbalance of oxygen supply. The consequence is momentary or permanent focal dysfunction of brain tissue.¹ According to Langhorne et al., strokes are classified into two subtypes, ischemic (80%) or hemorrhagic (15%), leaving 5% for all unspecified cases. That may be related to other diagnoses.² Another study reported that, of all strokes, 87% are ischemic, 10% are due to intracerebral hemorrhage, and the remaining 3% are due to subarachnoid hemorrhage.³

An ischemic stroke is the consequence of the occlusion of a blood vessel, also called a cerebral infarction. It occurs when the brain area loses blood supply due to clogging of the vessel that causes the interruption of blood flow, which generates the appearance of an infarcted area brain. This event is often due to decreased cardiac output or blood pressure, producing stenosis and its consequent low cerebral blood flow—a clot forms in one of the arteries that supply the brain, causing ischemia. The progression of ischemic brain damage after impaired blood flow involves the initial development of a core of irreversible injured necrotic tissue within the affected vascular bed, followed by the development of a late-phase lesion in the peri-infarcted area, a potential rescue area -penumbra area- which surrounds the affected area.^{4,5} The pathophysiology of ischemic brain damage involves activating deleterious signaling cascades. Deprivation of oxygen and glucose supply to brain tissue leads to immediate failure of ion pumps and channels, resulting in the release of potentially toxic concentrations of excitatory neurotransmitters, such as glutamate, which increases Ca²⁺ concentration. Intracellular, increased free radicals, and cytokine-mediated cytotoxicity, causing the death of vulnerable neurons.⁶⁻¹³

Hemorrhagic stroke is the least common type but the one with the highest mortality rate.¹⁴ It occurs when a blood vessel ruptures and bleeds into the brain, causing the death of thousands of neurons in a matter of minutes. Symptoms of hemorrhagic stroke include an arteriovenous malformation, aneurysm, or a rupture in the wall of a blood vessel. Hemorrhagic stroke represents approximately 10-15% of all strokes. Usually, metabolic stress and the generation of free radicals in the brain tissue cause the rupture of the blood vessels, resulting in infarction.¹⁵ Both types of ictus are potentially severe and are responsible for a large number of deaths and

disabilities in the world. Various studies have shown that various factors contribute to greater stroke risk. These factors include genetics, the gender of the person, age, diet, smoking, hypertension, and diabetes, among others. Many risk factors harm the cardiovascular system and can trigger stroke.^{16,17}

On the other hand, the most common disabilities in subjects who suffered a stroke are motor deficiencies such as paralysis and weakness of the extremities on the side opposite to the brain lesion, facial paresis, language, and speech disorders, altered levels of consciousness, and visual problems, among others.¹⁸⁻²⁰ All these disabilities drastically affect or reduce the quality of life of the subjects who suffered a stroke. This review will address the risk factors associated with stroke, the primary motor disabilities, and current and developing therapies used worldwide to reduce these disabilities and improve the quality of life of people who have suffered a stroke.

II. Incidence and prevalence of cerebrovascular accident

Stroke is a medical challenge and has a tremendous social and economic impact. According to the WHO, stroke represents the second cause of death worldwide, with 11% of all deaths, only after ischemic heart disease, which ranks first, representing 16% of all deaths worldwide.⁶⁵ In 2019, 6.6 million stroke-attributable deaths were recorded globally. Approximately 87% of strokes are due to ischemic infarcts, its prevalence increased significantly between 1990 and 2019, reporting an increase of 85%, mainly attributed to the decrease in population mortality and the improvement of clinical interventions.²¹ According to the Global Burden of Disease Study, the incidence of stroke increased by 70% in low- and middle-income countries between 1990 and 2019 but fell by 42% in high-income countries over the same period. The age of those affected, their sex, and their geographic location have increased the global economic and social burden of stroke.^{21,22}

On the other hand, various studies have reported that the incidence of stroke increases with age, especially after.²²⁻²⁶ However, the same studies reported a 12.9% increase in strokes in people aged between 20 and 54 between 1990 and 2016. Notably, the mortality rates due to stroke by age decreased by 36.2% in the same period.²³⁻²⁶ As for the incidence rates of stroke reported in 2019. It was found that China reported the highest rate, affecting between 331 and 378 people per 100,000 inhabitants.²³ Table 1 reports the stroke rates in different regions and countries.

Table 1. Incidence of cerebrovascular accident

| Reference | Country or Region | Incidence (cases/100,000 population) |
|--|-------------------|--------------------------------------|
| GBD 2016 Stroke Collaborators, 2019. ²² | Europe | 121-218 |
| GBD 2016 Stroke Collaborators, 2019. ²² | Latin American | 85-100 |
| GBD 2016 Stroke Collaborators, 2019. ²² | China | Between 331 y 378 |
| Madsen et al., 2020. ²⁷ | USA | 192 |
| Bahit et al., 2016. ²⁸ | Argentina | 201 |
| Parra-Cabrera, 2017. ²⁹ | México | 232 |
| Anderlini et al., 2020. ³⁰ | Australia | 117 |
| Cabral et al., 2016. ³¹ | Brazil | 83 |
| Vena et al., 2020. ³² | Spain | 244 |
| Meirhaeghe et al., 2018. ³³ | France | 257 |
| Wang et al., 2013. ³⁴ | United Kindom | 208 |

According to epidemiological studies of stroke, incidences of 800,000 cases were estimated in the United States in 2016³, and 1 million in the European Union in 2006.³⁵ In a more recent study, from 1990 to 2019, the absolute number of stroke incidences increased by 70% -range 67-73%-, the prevalence by 85% -range 83-88%-, also deaths associated with cerebrovascular accidents increased by 43% -range 31-55%-.²²

Estimators indicate that incidence of stroke will increase to 1.5 million per year in 2025 in the EU,³⁵ and projections for this region suggest that the proportion of the population over 65 years of age, the range of most stroke cases, will increase from 20% in 2000 to 35% in 2050. The projected population for Europe will decrease from 728 million in 2000 to 705 million in 2050, so the dependency ratio will change, and fewer young people will support an ever-increasing proportion of older adults. This will be a tremendous challenge for societies and health systems.³⁵ By 2030, projections suggest that 3.4 million people over 18 years of age will have a stroke, representing 20.5% of the population. The most significant increase is projected for the Hispanic population, which would reach 29%, according to the American Heart Association in 2016.³

On the other hand, it is essential to mention that some studies have predicted the absolute number of strokes for the year 2045, with an increase estimated 13% due to population aging.^{22, 36} In addition, recent research has shown that stroke survivors impose substantial direct and indirect costs of care, as well as costs due to lost productivity.³⁷ Some studies reported that stroke is the disease that contributes the most to generating disability in the world in people over 65 years of age.^{38,39}

In Mexico, stroke has gone from being the fourth cause of general mortality, reported in 2000, with just over 25,000 deaths, to the third cause of mortality, with more than 30,000 deaths in 2008. In this same period, it was the fourth cause of death in people over 65 and the seventh in subjects from 15 to 65 years of age. The

report from Health Metrics Evaluation Institute reports that from 1990 to 2010, stroke was among the first five causes of death in the country.⁴⁰ In 2018, according to figures from the National Institute of Statistics and Geography [INEGI], stroke ranked sixth in deaths in Mexico, with a total of 35,300 cases, of which; 17,841 were women and 17,459 men, and from January to June 2021, stroke ranked seventh in deaths.⁴¹ In 2010, stroke caused approximately 23,850 hospital admissions in patients of the Mexican Social Security Institute (IMSS), with a prevalence rate of 439.31 per 100,000 people over 60 years of age.⁴⁰ It is also important to note that in Mexico, the results concerning the quality of life evaluated in patients who survived a stroke show that the most affected dimensions are; everyday roles and physical function, and general health is also perceived as poor.⁴⁰

Feigin et al., 2017 estimated in 2013 that the prevalence of ischemic stroke in Mexico is 0-170 cases per 100,000 inhabitants and that there was a significant increase in the years of disability-adapted lives and deaths in developing countries such as Mexico.⁴² According to the Ministry of Health of the federal government of Mexico, in its epidemiological Health bulletins published weekly, from January 2018 to December 2021, 170,893 cases of stroke were registered, of which 53% were registered male and 47% female. Each year in Mexico, an average of 42,723 cases have been registered during the last four years.⁴³⁻⁴⁶

III. Risk factors associated with stroke

It is known that the risk of suffering a stroke increases with age, increasing the risk after the age of 55 in both sexes. Furthermore, it has been reported that the risk of stroke increases when the person suffers from comorbidities such as hypertension and hyperlipidemia. Some risk factors associated with stroke are described below, divided into modifiable and non-modifiable factors.

Modifiable stroke risk factors

These factors are considered relevant because adequate and timely treatment in susceptible people can reduce the risk of stroke. Risk factors include hypertension, diabetes, lack of physical activity, alcohol and tobacco abuse, hyperlipidemia, and diet.

Hypertension: It is one of the factors commonly associated with stroke. Some studies have reported that 54% of people with a stroke had a blood pressure of 160/90 mmHg or higher.^{47,48} One study reported that lowering blood pressure by approximately five mmHg decreased the relative risk of stroke by 40%.⁴⁹ Similarly, in randomized studies to reduce high blood pressure in subjects older than 60 years, the incidence of stroke was reduced by 40%.⁵⁰

Some studies have reported that hypertensive people had a higher risk for stroke OR: 1.91⁵¹, OR: 3.0⁵².

Diabetes: Some studies reported that diabetes increases the risk of ischemic stroke. These studies also reported that diabetes predisposes stroke subjects to severe disability and slower recovery after post-stroke interventions.^{53,54} Medical treatment and low-calorie nutrition decrease the risk of stroke and severe disability in people with diabetes.⁵⁵

Lack of physical activity: The lack of physical activity is associated with an increased risk of stroke and is related to other health problems such as increased blood pressure, obesity, and diabetes; diseases that, as mentioned above, are related to a high incidence of stroke.^{56,57}

On the other hand, physical activity reduces the risk of having a heart attack or a second stroke. Aerobic and muscular exercise helps stroke survivors to resume their daily activities and improve their quality of life. Finally, those who can exercise should do at least three days a week of aerobic activity, such as walking on a treadmill or using a stationary bike, and two to three times a week of strength training.^{58,59}

Alcohol: The relationship between alcohol consumption and stroke has been addressed by some studies. Low to moderate alcohol consumption was associated with a lower risk of ischemic stroke (≤ 2 standard drinks for men and ≤ 1 for women). Whereas high alcohol consumption was associated with an increased risk of suffering a hemorrhagic stroke.⁶⁰⁻⁶²

Tobacco: Tobacco use is one of the leading avoidable risk factors for stroke. Approximately 40% of deaths worldwide are caused by stroke in people under 65 and are related to smoking. Second-hand smoke exposure and smokeless tobacco use also increase the risk of stroke. Four to five years after quitting, a former smoker's risk of stroke is nearly identical to that of a never-smoker. There is a clear and well-defined causal relationship between tobacco use and stroke. Smoking increases the risk of stroke by two to four times in both men and women.⁶³⁻⁶⁹

The American Heart Association recommended that all adults be screened at each healthcare visit for tobacco use. Those who use tobacco should be assisted and strongly encouraged to quit.⁷⁰ Some studies have reported that smoking subjects had a higher risk of myocardial infarction (OR: 2.95) and stroke (OR: 1.67). These risks

were reported for 52 regions.^{71,72} Another study, carried out by Gyárfás et al., 2006, reported an odds ratio of 2.87, attributable risk of smokers to developing a cerebrovascular accident.⁵¹

Hyperlipidemia: Several studies reported elevated levels of total cholesterol were associated with the risk of stroke. However, high-density lipoproteins [HDL] decrease their incidence.⁷³⁻⁷⁵ In one study, it was reported that low HDL levels [<0.90 mmol/L], high total triglyceride levels [>2.30 mmol /L], and hypertension were associated with a twofold increase in the risk of stroke-related death in the population.⁷⁴ Lowering cholesterol levels with statin drug therapy reduces the risk of recurrent stroke by at least 12%.^{76,77}

Diet: Several studies have shown that a diet rich in fruits and vegetables reduces the risk of stroke. On the contrary, a poor diet increases the risk of a stroke, also contributing to other pathologies such as hypertension, hyperlipidemia, and diabetes. For example, excessive salt intake is related to arterial hypertension and stroke.⁷⁸⁻⁸²

Non-modifiable stroke risk factors

These include age, sex, ethnicity, and hereditary characteristics. Globally, the median age of stroke incidence was 70 years⁸³, and recent research has indicated that people ages 20 to 54 have an increased risk of stroke.⁸⁴ Women have the same or greater stroke risk than men, regardless of age.⁸⁵ Research shows that Hispanic and Black populations are at higher risk of stroke than white populations. In general, the incidence of hemorrhagic stroke is significantly higher in Black people than in age-matched white populations.⁸⁶⁻⁸⁸

Genetic factors

Genetic inheritance contributes as a risk factor for stroke. Genetic risk is proportional to the individual's age, sex, and race.^{89,90} Research has shown that family history, especially parents who had a stroke, increases a person's chances of developing the disease. A single gene mutation may contribute to pathophysiology in which stroke is the primary clinical manifestation, such as in autosomal dominant cerebral arteriopathy. This mutation was associated with subcortical infarcts and leukoencephalopathy and is the most common hereditary cause of stroke in adults under 65.⁹¹

Although the first case was described in 1955,⁹² the official characterization as defined in 1993, after the discovery of the responsible gene, the NOTCH3 gene on chromosome 19.⁹³ Also, stroke can be one of the many sequelae of multiple syndromes caused by genetic mutations, such as sickle cell anemia. In addition, some common genetic variants have been associated with an increased risk of stroke, such as the 9p2 gene polymorphism.⁹⁴ Recent evidence suggests that studying heritability will improve understanding of stroke subtypes, and patient management, and allow an earlier and more efficient forecast.⁹⁵

In a meta-analysis that included 7,388 cases and 254,798 controls in Europe, the USA, and Australia, five loci for lacunar stroke pathogenesis (COL4A2, LOX, SH3PXD2A, GPR126, HTRA1) were confirmed, highlighting their importance in the disruption of the vascular extracellular matrix.^{96,97}

Gender

Stroke in men and women largely depends on age. Its incidence is considered higher at younger ages in women, while it increases slightly with advancing age in men. Women's increased risk of stroke is due to pregnancy-related factors, such as preeclampsia, contraceptive use, hormone therapy, and migraine. Atrial fibrillation increases the risk of stroke in women over 75 years by 20%. Both cerebral infarction and intracerebral hemorrhage are common in men, but cardioembolic stroke, a more severe form of accident, is more frequent among women. The mortality rate from stroke is higher among women.⁹⁸⁻¹⁰⁰ Women live longer than men, which is one reason for their higher incidence of strokes.¹⁰¹ For men, the most common causes of stroke are smoking, excessive alcohol consumption, myocardial infarction, and arterial disorders.¹⁰²

There are differences according to the sex of the patients who survive a stroke.⁹⁹ A systematic review found 98 articles that contained crucial information regarding the sex in patients diagnosed with a stroke, highlighting that the mean age of those of the male gender was 68.6 years. In the case of women, it was 72.9 years, the incidence of stroke in the case of the male gender was 33% higher than that of the female gender, and the prevalence was 44% higher in the same relationship. The trend is that a stroke is more severe in the case of women, with a mortality rate of 24.7% one month after it occurs, versus 19.7% in men.⁹⁹

In the United States and other countries, women are less likely to be discharged from clinics -about the length of stay after the onset of stroke-; and are more likely to be referred to nursing homes for long-term care after a stroke. In Canada, Europe, and the United States, there appears to be no difference in access to physiotherapy, speech therapy, or occupational therapy for men and women; however, women do not experience the same recovery levels as men. For example, men and women improved after entering the rehabilitation program. However, men were approximately three times more likely to be independent in climbing stairs and performing activities of daily living - defined as the Barthel index ≥ 95 than women.¹⁰⁰

Hypothetically, these findings may be attributed to differences in muscle strength between men and women. However, it also becomes necessary to recognize that post-acute care outcomes and time to hospital discharge suggest a complex interplay of demographic factors, psychosocial functioning, pre-existing health status, and disease severity.¹⁰⁰

Due to disparities in outcomes associated with sex differences in recovery and outcomes after stroke, women need rehabilitation programs to focus more on improving their physical functioning and depression care, as well as increased social support and counseling.¹⁰⁰ Therefore, rehabilitation programs for stroke survivors must consider that there are substantial gender differences in the results achieved. Table 2 Reports the association of risk factors with stroke.

Table 2. Association between risk factors and stroke

| Reference | Risk Factor | Odds Ratios |
|--------------------------------------|-----------------------------|-------------|
| Gyárfás et al., 2006 ⁵¹ | Hypertension | 1.91 |
| Teo et al., 2021 ⁵² | Hypertension | 3.0 |
| Khan et al., 2022 ¹⁰³ | Hypertension | 5.86 |
| O'Donnell et al., 2016 ⁷² | Diabetes | 1.33 |
| Ke et al., 2021 ¹⁰⁴ | Diabetes | 1.6 |
| Khan et al., 2022 ¹⁰³ | Diabetes | 1.79 |
| Markidan et al., 2018 ¹⁰⁵ | Tobacco | 1.88 |
| | More than 11 cigarettes/day | 5.66 |
| Bailey et al., 2019 ¹⁰⁶ | Overweight/Obesity | 2.42 |
| Khan et al., 2022 ¹⁰³ | Hypercholesterolemia | 3.93 |
| Bailey et al., 2019 ¹⁰⁶ | Physical inactivity | 1.41 |

Stroke and socioeconomic situation

There is an inverse relationship between stroke and socioeconomic status attributable to inadequate hospital facilities and post-stroke care among low-income populations.¹⁰² A case study conducted in the United States of America showed that people with a high financial status had better post-stroke treatment options than disadvantaged people.¹⁰⁷ Another study in China linked low income and lack of health insurance with preventing a secondary stroke attack.¹⁰⁸ Similarly, research conducted in Austria associated the level of education with the adoption of treatments such as echocardiography and speech therapy. However, they found no difference in the provision of thrombolysis, occupational therapy, physiotherapy, or stroke care for secondary stroke according to socioeconomic status.¹⁰⁹ Notably, in the Scottish health system, essential treatments such as thrombolysis were provided regardless of the economic situation of the patients.¹¹⁰

Costs associated with stroke

During the years 2001 to 2005 in the United States of America, the average cost per patient of medical and rehabilitation services for the first year after hospital discharge was \$11,145, whereas the costs of rehabilitation services per year were \$7,318,283, three and it was estimated that they would increase to \$184.1 billion in the United States by the year 2030.^{111,112}

stroke also generates high costs for health systems. Multiple studies have evaluated the direct costs -related to medical care- of the care of patients with stroke. Demaerschalk et al. identified 28 studies that evaluated the direct costs of patients with ischemic stroke in the United States.¹¹³ Updating costs to 2008, mean hospitalization costs per patient ranged from \$8,000 to \$23,000, with one average stay hospitalization between 4.6 to 12.4 days. Regarding indirect costs, the volume of published information is lower. Evidence confirms that these make up the majority of the financial burden of stroke. Taylor calculated the indirect and aggregate costs of stroke in the United States in 1990.¹¹⁴ The indirect cost was \$23.6 billion, associated primarily with lost earnings from premature mortality and lost earnings in survivors. The added costs were estimated at 40.6 billion dollars associated with early care -first two years of onset of symptoms-long-term, outpatient care, and chronic care.

IV. Sequelae after stroke

Over a billion people around the world live with some form of disability. Of these, almost 200 million experience considerable difficulties in their functioning. This is a number that is constantly growing due to the aging of the population and the fact that older people have a greater risk of disability, and the global increase in chronic health problems associated with disability, such as diabetes, cardiovascular disease, and mental disorders. In future years, disability will be an even more significant concern as its prevalence is increasing.¹¹⁵ Chronic disease is estimated to account for 66.5% of the global measure of "years lived with disability" in low- and middle-income countries.¹¹⁶ a standard measure of the impact of disease on people's ability, is Years Lived with Disability or Disability Adapted Living [DALY].

One study found that, in 2010, stroke increased Disability Adapted Life Years by 19% over the period 1990 to 2010,¹¹⁷ and more recently, over the years 1990 and 2013, it was estimated that people who survived a

stroke added 113 million Disability Adjusted Life Years.⁴² Finally, worldwide, in the period from 1990 to 2019, the DALYs associated with stroke increased by 32% -range of 22-42%.²²

Stroke patients may experience various limitations and complications that may hinder optimal recovery. Mentioned below are some of the central sequelae reported in stroke patients. The most frequent problems are total or partial motor deficits, sensory disturbances, language disturbances, fatigue, osteoporosis, shoulder pain, falls, fractures, spasticity, urinary incontinence, hemiplegic shoulder subluxation, depression, anxiety, dementia, and memory impairment. Many of these affectations prevent the person from carrying out activities of daily living such as climbing stairs, getting dressed, and going to the bathroom, compromising their social and work reincorporation, causing incredible frustration in the person who suffers from it.

As previously mentioned, stroke is the leading cause of disability and death in Western countries.¹⁰⁸ The most common and widely recognized neurological deficit associated with stroke is a neurological compromise, ranging from loss of motor function to performance limitation.¹¹⁸ Said motor compromise can affect facial and extremity movements, reaching 30% of cases to prevent independent walking permanently. In consideration of the above, the administration of interventions that reduce disability and increase the probability of obtaining good functional performance -including physical therapy- could help reduce the burden of disease.¹¹⁸ There is considerable variability in the effectiveness of physical rehabilitation strategies in patients with acute stroke.¹¹⁸⁻¹²³ Analysis of the best available evidence on the benefits and risks of each of these strategies will enable the clinician to provide the safest and most effective therapeutic approach for their patients.¹¹⁸

V. Conclusion

Many factors can increase the risk of having a stroke. Potentially treatable and preventable risk factors for stroke include obesity, physical inactivity, smoking, hypertension, and high cholesterol levels, among others. Therefore, it is required to have healthy lifestyle habits. Diet, exercise, and weight loss can help reduce blood pressure, excess weight, and cardiovascular disease, thereby reducing the incidence of stroke. Over the years, significant advances have been made in understanding the etiology of stroke in identifying and preventing risk factors. However, these advances do not occur uniformly throughout the world. Therefore, new strategies must emerge to obtain optimal results in preventing and treating stroke. In addition, the development of new tools and intervention therapies is intended to improve the outcomes of stroke survivors. In addition to enhancing treatments' cost/benefit ratio and helping people who have suffered a stroke enjoy a better quality of life.

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