

RESEARCH PAPER

Stroke pathogenesis: Biophysical Mechanisms and Risk factor linked with Disease progression

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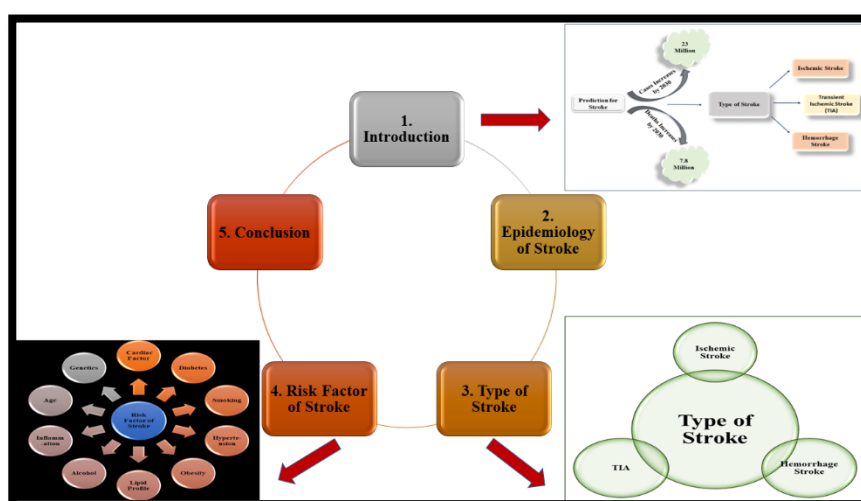
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ABSTRACT

Stroke is the world's largest contributor to long-term disability as well as the subsequent primary cause of death. The burden of stroke is rising globally as the population increases and risk factors such as heart disease, smoking, diabetes, hypertension, obesity, lipid profiles, alcohol, inflammation, age, and genetics continue to rise and be poorly managed. The development, diagnosis, and treatment of stroke are thought to be significantly influenced by biophysical variables. This review article's goal is to outline the risk factors and biophysical mechanisms that put a person at risk for stroke.



Keywords: Drug Repurposing, Knowledge Graph, Graph Neural Network, Typed Path Algebra, Heterogeneous Graph, Drug Module.

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1. INTRODUCTION

The second most frequent cause of mortality is stroke, and disability globally, and middle-class and low-income nations bear the brunt of the disease's impact [1]. Due to the significant risk that stroke poses to people's health and wellbeing, it has drawn a lot of attention. The number of stroke fatalities and cases is predicted to rise to 23 million and 7.8 million, respectively, by 2030 [2] as shown in figure 1. Among the most common causes of death and a medical disease that impairs both physically and psychologically is stroke. According to the World Health Organization's

(WHO) official data, 15 million individuals worldwide are estimated to experience a stroke each year. Three types of strokes exist: hemorrhagic stroke, transient ischemic attack (TIA), and ischemic stroke (IS). Eighty to ninety percent of stroke cases are thrombotic and embolic events, which cause disruption of blood flow and lead to ischemic stroke. A TIA, or transient ischemic attack, is characterized by brief episodes of thrombotic embolism that momentarily impede blood flow, while a hemorrhagic stroke results from a blood vessel rupturing, resulting in blood leaking. Although TIA-related damage is less severe than with the other two

disorders, it can escalate into a potentially fatal and irreversible danger of ischemic and hemorrhagic strokes [3].

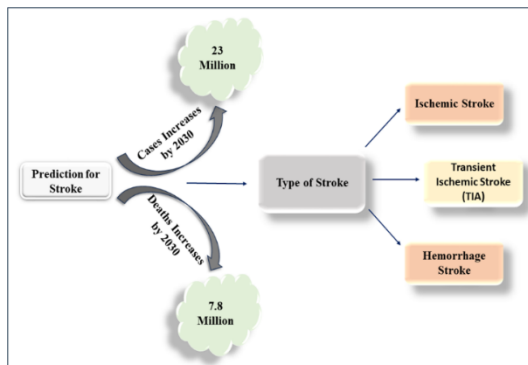


Fig. 1: Type of stroke and its futuristic effect

The sudden blockage of cerebral blood flow that results in an ischemic stroke is a fatal neurological condition. Those over 25 have a lifetime risk of 24.9% for stroke [4]. The oxidative damages caused by excessively created ROS (reactive oxygen species) following a stroke will significantly destroy the cerebral vasculature and neuronal networks, along with the symptoms of ischemia harm and disturbance of the blood-brain barrier (BBB) [5]. Twenty to twenty-five percent of all stroke events occur from intracerebral hemorrhage (ICH), a severe type of stroke in which less than forty percent of affected individuals survive after a year [6]. Intracerebral bleeding can occur when vessel wall integrity is compromised, which can have serious consequences. The amount of extravasated blood is one of the most significant indicators of functional prognosis in individuals with hemorrhagic stroke. While hemostatic medications have shown promising outcomes in hemorrhagic stroke patients, increasing the endogenous hemostatic system can stop cerebral hemorrhage [7]. A transient incident of focused neurological impairment lasting less than 24 hours that is not linked to a persistent cerebral infarction is the classic definition of a transient Ischemic attack (TIA) [8]

Numerous studies conducted recently have verified that materials with nanotechnology can transport targets for drugs across the blood-brain barrier, perform secondary targeted medication administration, and release the medication into the injured cells and tissue in an ischemic stroke. As a result, nanomaterial's have a lot of potential for improving ischemic stroke treatment [9]. Therapeutic agents can now be delivered across the BBB with the help of safe and efficient nanomedicine delivery devices, which have drawn some interest recently. Their limited success is caused by their capacity to cross the blood-brain barrier through both active and passive targeted techniques, which leads to increased build-up in the brain [2]. Nanomaterials are being used as nanomedicines in the last few years and are essential for the diagnosis and therapy of many neurological illnesses throughout the world [10]. According to definitions, a nanomaterial is any material having one or more exterior dimensions between 1 and 100 nm that has distinct thermal, optical, magnetic, and electrical

characteristics from their bigger counterparts [11]. Scientists in the fields of chemistry, biology, physics, and engineering have shown a great deal of interest in these unique qualities, which are linked to quantum effects or the high surface to volume ratio of nanoparticles [12]. They are appropriate for a variety of applications due to their distinctive optical, electrical, and magnetic features [13].

2. EPIDEMIOLOGY OF STROKE

Strokes affect around 15 million people worldwide each year, resulting in 33% lifelong disability and 40% death [14]. Strokes are the second largest cause of mortality worldwide. It kills around 5.5 million and affects 13.7 million people yearly. Ischemic strokes are responsible for approximately 87% of all strokes, a figure that climbed significantly between 1990 and 2016, due to reduced mortality and improved treatment administration. First-time or primary hemorrhages make up the bulk of strokes, having subsequent hemorrhages (second-time) accounting for roughly 10–25%. The prevalence of stroke rises with age, doubling after 55 years. Strokes among individuals aged 20 to 54 years, on the other hand, grew from 12.9% to 18.6% of the total events worldwide from 1990 to 2016. China is the country with the highest recorded stroke incidence, impacting roughly 331-378 individuals for every 100,000 years of life. The second-highest incidence (181–218 per 100,000 life years) is seen in Eastern Europe, while the lowest rate is found in Latin America (85-100). Stroke incidence in both men and women is also age-dependent. Women are more likely to encounter it at a younger age, whereas men see a minor rise with age. The greater risk of stroke in women is attributable to variables connected pregnancy-related conditions such preeclampsia, contraception usage, hormonal medication, in addition to migraine with aura. Tobacco smoking, vascular disease, myocardial infarction, and high alcohol consumption problems are among the main reasons why men have strokes [15].

3. TYPES OF STROKES

Strokes are classified into numerous categories, including: Transient ischemic attack (TIA), hemorrhagic stroke, and ischemic stroke given in figure 2.

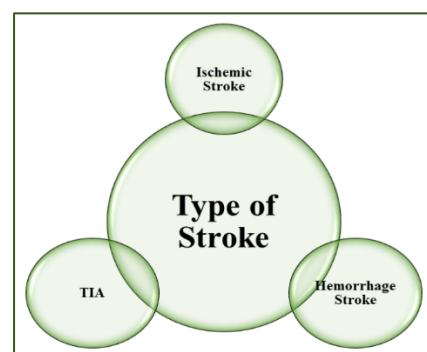


Fig. 2: Classification of stroke

3.1 Ischemic Stroke

The most frequent form of stroke, caused by a blocked blood artery in the brain. A blood clot or plaque accumulation may create this obstruction [16]. Symptoms include numbness, weakness on one side of the body, visual disturbances, dizziness, balance issues, disorientation, and headaches.

3.2 Hemorrhagic Stroke

Caused by bleeding in or around the brain, generally as a result of a ruptured blood vessel. Uncontrolled hypertension, ruptured arteries, and arteriovenous malformations (AVMs) can all contribute to hemorrhagic strokes [17]. The signs include numbness and loss of function. Hemorrhagic strokes typically have a quick start, such as a severe headache [18].

3.3 Transient ischemic attack (TIA)

When the blood supply to the brain, retina, or spinal cord is momentarily cut off, a transient ischemic attack (TIA), often known as a mini-stroke. TIAs can create brief stroke-like symptoms, although they do not harm brain cells or cause lasting impairment [8].

4. RISK FACTOR OF STROKE

Several medical and behavioral problems have been associated with a higher risk of stroke. These variables consist of, but are not restricted to, food, diabetes, high blood pressure, and smoking patterns. Numerous risk factors in figure 3 have a detrimental influence on the heart, which is usually the best approach to estimate risk of stroke.

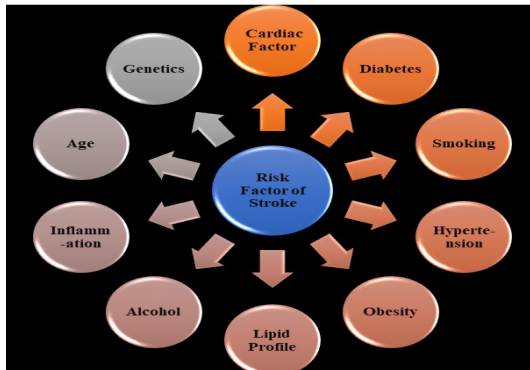


Fig. 3: Risk factor of responsible for stroke

4.1. Cardiac Factor

The infarction of the heart, mostly Atrial fibrillation, is the most serious cause of ischemic stroke, leading to significant disability and fatality. The existence of AF rises with age, accounting for 20-25% of strokes in individuals over eighty years old. Anticoagulant medication is particularly successful in avoiding stroke in persons with AF (relatively lower risk of around two-thirds) [8].

4.2. Diabetes

Twenty percent of diabetes-related deaths are due to stroke [8]. Your body cannot effectively metabolize food if you have diabetes. Blood glucose, or sugar, builds up when your body is unable to produce enough insulin or uses it improperly [19]. Over time, high blood sugar can damage

the body's blood vessels, increasing the risk of stroke [20].

4.3. Smoking

Smoking increases the risk of stroke because it reduces blood oxygen levels and raises blood pressure. Furthermore, smoking thickens blood [21]. This raises the possibility of blood clots developing even more.

4.4. Hypertension

This is the most significant stroke risk factor that can be changed. Nearly half of all victims of stroke, and an even larger a percentage of people with ICH have a history of high blood pressure. Even among persons who are not classified as hypertensive, increasing blood pressure increases the chance of a stroke. This makes hypertension detection and treatment critical for stroke prevention on both the main and secondary levels. The actual danger posed by high blood pressure diminishes past the age of sixty, when it gives a non-significant contribution at age 80 with a relative risk of 3.5 [8]. When a section of the brain does not receive enough nutrition and oxygen. Additionally, it could happen if there is bleeding within or near the brain [22]. These disorders trigger brain cell death.

4.5. Obesity

Cholesterol, blood pressure and levels of glucose account for the majority of the relationship between BMI and stroke risk; those who engage in physical activity have a lower probability of stroke and total stroke death compared to individuals who aren't [8].

4.6. Lipid Profile

Human Beings lipid profiles are now being investigated, encompassing both standard and non-traditional lipid profiles, particularly as separate indicators of heart disease. Some studies have found that cholesterol that is low-density lipoprotein, cholesterol that is non-HDL-C, and the TC/HDL-C ratio are all important indicators of CVD [20].

4.7. Alcohol

A lower risk of ischemic stroke is associated with light to moderate alcohol consumption (<4 units/day), whereas greater quantities are linked to an elevated danger. Alcohol use is directly proportional to the chance of developing ICH. Recreational substances such as cocaine, amphetamines, heroin, cannabis, and ecstasy increase the risk of stroke, especially ischemic stroke and intracerebral hemorrhage [8].

4.8. Inflammation

Inflammatory indicators are linked to a slightly higher risk of arteriosclerosis and stroke. Vaccination against influenza has been linked to decreased stroke rates. COVID-19 has been associated to major vascular occlusions, as well as an increase in inflammation and coagulation [8].

4.9. Age

This is the most significant contribution to stroke risk. After

age 55, the incidence increases by doubling every decade [8].

4.10. Genetics

Family history of stroke (FHS) is a significant risk factor for the emergence of stroke [23]. In addition to stroke-related single-gene illnesses (Fabry's disease, connective tissue disorders, homocystinuria, sickle cell disease, CADASIL, and CARASIL). The MEGASTROKE collaboration found 32 important genome-wide loci, including 22 unique ones. Some loci were substantially linked to stroke processes, including cardiac embolism, small artery disease, and large artery disease. However, half of the loci had a genetic connection to more vascular disorders, has the strongest association for blood pressure [8].

5. BIOPHYSICAL MECHANISM OF STROKE

The hemodynamic and biophysical processes underlying the blockage vary in terms of blood flow, even though the outcomes of both hemorrhagic and ischemic strokes are similar in that a blockage in a vessel and the ensuing reduced blood supply to the brain can cause neurological impairments and possibly death. Vasospasm, hemorrhage, thrombus, atherosclerosis, embolus, and lowered systemic pressure are the six different biophysical mechanisms shown in figure 4 that can result in blockages that eventually cause stroke [24].

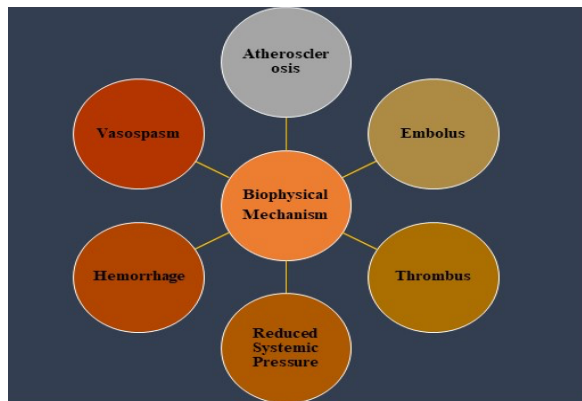


Fig. 4: Biophysical Mechanism of stroke

5.1 Atherosclerosis

The degenerative process known as atherosclerosis, or "hardening of the arteries," occurs when fatty deposits or hardened lipid from the circulating blood build up going around the innermost intimal layer of the arterial wall [25]. Nearly all major bifurcations, such as atherosclerotic plaques on the carotid outer one or both daughters' wall (hip) vessels. A variety of distinct metabolic activities, namely low-density lipoprotein oxidation, the production of streaks of fat, and the proliferation of cells in smooth muscle, result in atherosclerosis and the development about arterial plaques [26]. The lumen gets thinner and the walls get thicker, calcify, and become fibrotic as the plaques develop, reducing the volume of blood that reaches the tissues the artery serves [24].

Due in part to restrict flow and high shear pressures that the

blood applies to the artery wall, deposits of atherosclerosis encourage the formation of thrombi or the procedure of thrombosis [27]. An artery's inner wall may be mechanically damaged by high wall shear stress, which could start a lesion. Conversely, low shear stress on the wall may promote the formation of plaque by encouraging the deposition of particles on the arterial wall. Because turbulence can raise the amount of kinetic energy that is deposited in the vessel walls and generate pockets of stopped blood flow, or stasis, which it has been connected to atherosclerotic disease and has been shown to promote clotting. Due in part to flow restriction and the high shear pressures that the blood applies to the artery wall, deposits of atherosclerosis encourage the formation of thrombi or the procedure of thrombosis. A lesion could be caused by high wall shear stress injuring the inner wall of the artery mechanically [24]. Conversely, minimal shear stress on the wall may promote the formation of plaque by encouraging particle deposition of particles on the arterial wall [28]. Because turbulence can raise the amount of kinetic energy stored in the walls of the vessel and create pockets venous stasis, or halted blood flow, has also been connected to atherosclerotic disease and promotes clotting [29].

5.2 Embolus

An embolus is a moving "clot" of gaseous or particle debris, such as atheromata. A platelet aggregate that has come loose from an atherosclerotic lesion is a typical example of an emboli. The bloodstream carries the dislodged platelet accumulation throughout the brain's circulatory system until it reaches capillaries that are too tiny for it to spread further. The clot clogs the vessel and stops blood flow to the distal arteries because it has nowhere to go [24]. Even though the carotid arteries and related cerebrovasculature are the main focus of our current discussion, Emboli may come from far-off places like the lungs, peripheral circulation and the heart [30]. Eventually, these emboli might move through the cerebral blood arteries, blocking blood flow and leading to stroke. Additional causes of emboli consist of valvular disease and fibrillation in the atrium [31]. The amount of the embolus and the obstruction's placement determine how severe the stroke is. The area of the brain that is at danger increases with the embolus's magnitude and the vascular obstruction. Emboli account causes almost 31% of all instances of stroke [32].

5.3 Thrombus

The internal physiological mechanism that causes blood to clot is called thrombosis. A blood clot is called a thrombus, a collection of platelets and fibrin that develops in reaction to a vascular injury or an atherosclerotic lesion [33]. When an artery or tissue is injured, the blood coagulation system is triggered. This sets off a series of events that change prothrombin and produce a fibrin clot: Prothrombin → Thrombin → Fibrinogen → Fibrin → Fibrin Clot [34]. Vessel injury can result from Shear strains, or pressures combined using the extra energy produced via the turbulent flow applied against the vessel wall's inner (intimal) lining, especially The wall of an atherosclerotic vessel, though

there are many different mechanisms and causes of vessel injury. Thrombi are responsible for about 33% of all stroke cases [24].

5.4 Reduced Systemic Pressure

Localized areas of the cerebral arteries are affected by the previously mentioned processes of blood flow restriction that result in stroke. It is assumed in this instance that the heart is operating normally under appropriate systemic pressure [35]. Atrial fibrillation and myocardial infarction are examples of cardiovascular disorders that weaken the heart wall and cause anomalies in the heartbeat's physiological function. These conditions eventually lead to decreased systemic pressure and ischemia [36].

5.5 Hemorrhage

Generally speaking, blood arteries are structurally capable to withstanding the dynamic amounts needed to sustain circulatory activity. The vessel wall may grow tired, abnormally weak, and possibly burst for unknown reasons [24]. Hemorrhage happens when a Blood can seep into the surrounding brain tissue when an artery bursts. The blood, now thrombosed, eventually compresses the surrounding veins as it builds up inside the brain due to the displaced volume [37]. The insult is made larger by vessel compression, which results in a decreased diameter of the vessel and a matching decrease flowing to the tissue around it [38]. Aneurysms and arteriovenous malformations (AVMs) are two vascular abnormalities that can cause hemorrhagic strokes [39].

5.6 Vasospasm

Cerebral vasospasm is a muscle contraction that can cause the subarachnoid space's arteries to become spastic when bleeding takes place there. Vasospasm-induced contraction can result in a localized constriction severe enough to result in complete blockage [24]. The vessel may contract for hours or days at a time due to vasospasm [40]. But regardless of how long of vascular constriction that occurs during vasospasm, reduced blood flow results in cerebral ischemia, which is believed to be reversible during the first six hours, after which it is irreversible [41]. Vasospasm has been demonstrated to happen up to two weeks following subarachnoid hemorrhage, peaking five to ten days later [24].

7. CONCLUSION

Despite this, during the past ten years, we have learned more about the epidemiology of stroke. Human stroke risk is predicted to increase dramatically over the next few decades, and by 2030, stroke cases, fatalities, and disability-adjusted life years (DALYs) are predicted to climb greatly worldwide. The clinical genesis and several factors are implicated in the etiology of stroke but a number of elements acting either singly, either consecutively or in combination. These variables may include biophysical, biochemical, and genetic elements. Nonetheless, it is thought that biophysical parameters are important in the onset, treatment and diagnosis of stroke. The biophysical

mechanism, risk factor, types and epidemiology of stroke were the main topics covered in this review.

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Author contributions

Conceptualization and design: PB, PK, RK Data curation and formal analysis: PB, VP, DS, PPS, SKM, R, RK; Investigation and Methodology: PK, VP, DS, RK, Manuscript writing and editing: All authors; Project administration and supervision: PB, RK.

Conflict of interest

The authors declare no conflict of interest.

Data and Code

Not Applicable

Ethical approval

Not Applicable

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