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Review on Mechanistic Pathways and Risk Factors of Cerebral Ischemia

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ABSTRACT

Cerebral ischemia is a brain injury caused by a sudden stoppage in the blood supply to the brain. It occurs when part of the brain does not receive the needed blood flow for one of two reasons either the blood supply to part of the brain is suddenly stoppage or rupture of brain blood vessels. In this review article, we present the recent focusing on mechanism of cerebral ischemia especially the involvement of neuroinflammation, excitotoxicity, reperfusion, free radicals, oxidative stress in reperfusion injury, blood brain barrier disruption, apoptosis, role of platelet and stroke risk factors are described. In the present paper, we have discussed the recent research on the mechanistic pathways and risk factors involved in cerebral ischemia. We consider that understanding the cerebral ischemia will allow the development of novel treatment interventions.

1. INTRODUCTION

Cerebral ischemia is a predominant form of stroke induced by disruption of cerebral blood supply leading in rapid energy depletion and death of cells [1]. Ischemia leads to brain metabolism changes, metabolic rate reductions, and energy crisis [2]. Ischemic stroke is a prevalent and disabled disease that affects more than 690000 adults in US annually [3]. A first or repeating stroke happens at regular intervals, influencing around 800000 individuals every year. Stroke happens when a blood coagulation/thrombus or vein rupture (i.e., hemorrhage) achieved by arteriovenous transformations or aneurysms meddles with the vein. Because the brain is one of the most energy-intensive organs, the lack of oxygen and the supply of nutrients can cause serious brain damage leading to neurological disorders [4].Intracerebral haemorrhage (ICH) impacts more than 1 million people all around yearly and is the most fatal and debilitated type of stroke [5, 6]. Regardless of how ICH treats just 10–15% of all strokes in the U.S., it induces a lack of nutrition and mortality [7].

The consequence of expanding intracellular Ca++ is an upregulation of an assortment of compound frameworks, for example, lipases, proteases, and endonucleases [8]. Free O2 radicals are thus formed through a number of biochemical pathways, and apoptotic cell death. Free radicals also cause a variety of inflammatory mediators, such as platelet and endothelium selectins, particle collection, platelet founding factor, tumor putrefaction factor alpha, and interleukin social affair. It is essential to understand such complicated pathophysiology of sub-atomic and cell occasions resulting from ischemia in full consideration of the fact that one of the aims of using animal models of cerebral ischemia is to isolate these various parts of harm to arrive at a potential target location for ischemial damage treatment (i.e., neuroprotection) [9].

2. MECHANISM OF CEREBRAL ISCHEMIA

Cerebral ischemia is generally categorized into global ischemia and focal ischemia. Classification of ischemia models shown in Figure 1. There are different mechanisms are involved in Cerebral Ischemia and some are listed in the following Figure 2.

2.1. Neuroinflammation

Inflammation is viewed as a noteworthy supporter of ischemic injury [10, 11]. The focal occasion in post ischemic aggravation is enrollment of leukocytes, first neutrophils, and after

that a flood of cells of the monocyte/macrophage [11,12]. The nearness of damaging leukocytes in the brain parenchyma can upgrade ischemic damage, yet they additionally further intensify the provocative response [13]. During ischemia/reperfusion the brain produces chemokines, for example, CXCL8 (otherwise called interleukin-8), CCL2 (MCP-1), CCL3 (MIP-1 α), CCL4 (MIP-1 β), CCL7 (MCP-3), CX3CL1 (fractalkine), and CXCL10 [14,15]. Chemokine explanation is immovably related with infarct size and the development of ischemic sores. Control of chemokine verbalization/development impacts ischemic cerebrum injury [14, 16]. Tissue damage starts after a few hours of the onset of ischemia with an inflammatory response, a typical cerebral parenchyma reaction to various types of attack. This involves leukocyte penetration, both polymorphonuclear leukocytes and monocytes/macrophages (but not lymphocytes), which are the cell arbiters of the resulting obstacle to small-scale channels, edema growth, cell fragmentation, and tissue necrosis. This provocative damage is affected by explicit atoms consolidating particles of the cell bond (selectins, integrins, and immunoglobulins), cytokines (IL-1, IL-6, TNF-α, and TGF-β), chemokines (CINC, MCP-1), inducible neuronal nitric oxide synthase (iNOS) transmitted by endothelial cells, requested astrocytes, microglial cells and leukocytes (granulocytes, monocytes/macrophages, and lymphocytes) and these leukocytes. Cell attachment particles intervene cell to cell cooperation for leukocyte movement. Neutrophil enlistment in ischemic brain starts with neutrophil passing on actuated endothelial vein dividers, interacting with selectins, trailing through neutrophil initiation and adherence, interceding with integrins and immunoglobins. Neutrophils migrate into the brain parenchyma, a practice that is supported by BBB disruption when clot to brain-vein divisions. The enlistment of neutrophils can impede microcirculation and prevent blood from regenerating after reperfusion. After ischemia, this blockage can cause additional damage of tissue. By discharging proteolytic compounds and oxygen-free radicals, when neutrophils enter the ischemic brain, they inflict tissue damage. Therefore, selectins containing P-, E-, and L-selectin are glycoproteins. Intracellular grip particles like ICAM-1 and ICAM-2, vascular cell attachment atom 1 (VCAM-1; CD106), platelet-endothelial cell attachment atom 1 (CD31), mucosal position in cell attachment particles 1 (CD146). In contrast, cytokines and chemokines contribute to the brain damage associated with the stroke. For example, cytokines, interleukins (IL-1, IL-6), tumor narcosis factor (TNF-α, TGF-β) and chemokines, cytokine-initiated neutrophil chemoattractant (CINC) and monocyte chemoattractant protein–1 (MCP-1) are produced during ischemia through a variety of endothelial cell types including microglia, neurons, platelets, leukocytes and fibroblasts. IL-1's possible negative impacts include fever,

arachidonic corrosive discharge; excitotoxicity and nitric oxide mixture development interfered. All IL-1, TNF-α stimulates the articulation of attachment particles in cerebral endothelial cells as well as the aggregation and transmigration of neutrophils. In contrast, TNF-α enhances extreme protein production stage, blood-brain barrier disruption, and allows other fiery arbiters to be recruited. Nonetheless, in the pathogenesis of stroke, TGF-β anticipates neuroprotective function [17].

2.2. Excitotoxicity

It is broadly acknowledged that glutamate is engaged with the advancement of ischemic cell damage. It is discharged during ischemia from the intra-cell into the extracellular space, assumes a significant job in the improvement of the ischemic cell damage activated by transient overall cerebral ischemia. Glutamate by then ties to inotropic glutamate receptors, and hence begins sodium and calcium flood into the cell. The sharp increment in intracellular calcium movement during ischemia causes neuronal damage by an over activation of a course of calcium-subordinate catabolic procedures, for example, lipolysis and proteolysis [18].

2.3. Reperfusion

Reperfusion is portrayed by starting blood supply containment, which is followed by vascular reclamation and accompanying downstream tissue reoxygenation. Regardless of relieving hypoxia of the introductory tissue, tissue damage can worsen. It happens in both global hypoxic damage and auxiliary stroke focal ischemic injury.

A break in the bloodstream to the affected tissue accompanied by intake of cell energy resources and anaerobic substratum level glycolysis, thereby finding lactic acidosis, irritation of sodium-potassium pumps, glutamate intake, cytotoxic edema, free extreme arrangement and depiction of both inborn and elastic in vulnerable responses [19].

Hemorrhagic change of ischemic dead tissue is maybe the most well perceived result of ischemia, trailed by reperfusion. The interruption of BBB and subsequent edema, neuroinflammation and proceeded with damage interceded by free extreme oxides add to the hemorrhagic change of ischemic tissue beds following the arrival of bloodstream to the region which once experienced confinement [20].

2.4. Free radicals

Oxygen-free radicals have been suggested for some time to add to ischemic brain damage [21]. Oxygen radicals are produced during reperfusion. Radicals are unpaired particles that carry electron in their outer orbital ring. The concept that oxygen radicals may be important mediators of brain damage related to ischemia and reperfusion [22].

It is known that oxidative brain damage contributes significantly to ischemic brain injury. The supply of glucose and energy to the neurons is interrupted after a stroke, leading to necrotic cell death and an infarction. Neurons in the encompassing obscuration are provided with blood by security supply routes and in this way, may stay practical for an all-inclusive period if bloodstream return. In any case, during this reperfusion phase, reoxygenation also occurs as a substratum for various enzymatic oxidation responses generating ROS and resulting in deferred neuronal damage along these lines. There is proof that the arrival of ROS and expanded lipid peroxidation can be identified at an early and late time-purpose of I/R damage, the wellspring of ROS delivered under various periods of the damage was not investigated in detail. Sources, for instance, cyclooxygenase-2 (COX-2) and debilitated mitochondrial limit can provoke the appearance of ROS in the brain during cerebral ischemia and reperfusion. Mitochondrial calcium over-burden and a penetrability change of the internal mitochondrial film have been appeared to assume a significant underway of ROS by the mitochondria. It has likewise been indicated already that hypoxia triggers the change of NAD-decreasing xanthine dehydrogenase to the oxygen radical-creating xanthine oxidase in granulocytes. During ischemia, over the top ATP utilization prompts the aggregation of the purine catabolites hypoxanthine and xanthine, which upon consequent reperfusion and overflows of oxygen, are used by xanthine oxidase to yield enormous measures of superoxide and hydrogen peroxide. Within the sight of iron, superoxide anion and hydrogen peroxide respond through the Haber-Weiss response to shape hydroxyl radicals. Along these lines, this profoundly responsive radical at that point start lipid peroxidation of cell membrane parts and the consequent arrival of substances that select, actuate and advance the leukocytes adherence to microvascular endothelium. Thus, the adherent leukocytes at that point bring about additional endothelial cell damage through the arrival of ROS and different proteases. The free radical generation includes different pathways, for example, XO pathway, COX pathway, NO pathway and polyol pathway [23].

2.5. Oxidative stress in reperfusion injury

The oxygen molecule is basic to aerobiosis being the last acceptor of electron in the respiratory chain of mitochondria and in the combination of ATP through oxidative phosphorylation. Be that as it may, a solid case can be made for atomic oxygen noticeable all around we inhale being the most risky poison and cancer-causing agent in the earth as a result of its tendency to produce free radicals. It has been exhibited that roughly 2% to 5% of the electron flow in disconnected brain mitochondria produces superoxide anion radicals and hydrogen peroxide. During brain ischemia, intense oxygen and glucose hardship prompts failure of neurons to integrate adequate ATP from oxidative digestion. This energy loss triggers neuronal passage through a few merging components, including oxidative pressure, excessive ionic pump action prompts aggregation of Na+ and Ca2+ intracellular, which leads in turn to cell expansion and necrosis. Additionally, these particles depolarize influenced neurons, prompting extreme arrival of the excitotoxic synapse glutamate. Initiation of glutamate receptors compounds metabolic disappointment and putrefaction and furthermore upgrades the generation of ROS by invigorating master oxidant proteins. NOS1, or neuronal NOS (nNOS), is a Ca2+dependent chemical and is subsequently enacted during Ca2+ over-burden found in ischemia. Neighboring neurons and non-neuronal cells likewise contain prooxidant chemicals that are Ca2+dependent (for example xanthine oxidase) or autonomous [e.g. cyclooxygenase 1 (COX-1), COX-2, and NAD(P)H oxidase], prompting creation of O2- in the ischemic brain. Superoxide, NO-and ONOO-then oxidize lipids, proteins and DNA, killing incorporating neurons by necrosis, adding to oxidative stress [24].Mechanism of cell damage and cell death in ischemic injury shown in Figure 3.

2.6. Blood brain barrier disruption

Hypoxic damage of vascular endothelium, toxic damage of inflammatory particles, free radicals and particularly destruction of the basal lamina by grid metalloproteinase are potential reasons for BBB interruption which prompts vasogenic edema, aggravation and probably hemorrhagic entanglements after stroke. Transient ischemia by the postponed reclamation of bloodstream appears to bother infraction basically because of extra BBB damage [25].

2.7. Apoptosis

Activated by various procedures, including excitotoxicity, free extreme development (damaging cell lipids, proteins and nucleic acids), irritation (initiation of FAS receptor, for example through authoritative of tumor corruption factor-alpha; TNF-α), mitochondrial and DNA harm and cytochrome-C discharge from mitochondria. Apoptosis happens after milder ischemic damage, especially inside the ischemic obscuration. Necrotic cells become edematous and lose their cell structure by cytoskeletal breakdown. Apoptotic cell is described by various morphological highlights: shrinkage of the cytoplasm, stamped buildup of chromatin, film blebbing and fracture of the cell [26].

2.8. Role of platelet

In clinical stroke, platelet accumulation prompting vascular thrombosis and resulting embolization are basic engaged with the generation of ischemic affront. Abnormal platelet capacity is found in patients in danger for stroke and following transient occasions. Platelets may gather in zone of unusual stream qualities, including heart valves and explicit cerebral supply routes branch focuses. Platelet occasions can prompt extreme however transient hemodynamic irritations that may bring about gentle, moderate or serious morphological changes. Transient platelet collection can likewise prompt vascular changes, including spillage of BBB and irregularities in vascular reactivity. Platelet initiation triggers arrival of thick granule constituents including adenine nucleotides, thromboxane A2, calcium and serotonin, prompting practical changes inside the vascular endothelium and critical vasoconstrictive results. Clinical examinations exhibit expanded thick granule emission, platelet arrival of microparticles, platelet actuation in subtypes of ischemic stroke, increment in mean platelet volume and platelet cytosolic Ca2+ discharge middle people that may cause chemotaxis and movement of leukocytes, in this way fueling the inflammatory response. These instruments may likewise demonstrate to be significant in cerebral reperfusion damage after ischemic stroke [27].

3. STROKE RISK FACTORS

Approximately 90% of stroke risk, modifiable-changing factors of risk such as high blood pressure, obesity, hyperglycemia, hyperlipidemia and renal dysfunction can be linked to analyzes using GBD (Global burden of disease) data, and 74% to behavioral risk factors, for example, smoking, sedentary life and unsanitary diets [28]. Globally, 29% of the risk of

stroke was attributable to air pollution. The list of risk factors related to cerebral ischemia are shown in Figure 4.

3.1. High BP

BP is an important threat determinant for intracranial and ischemic stroke. The evidence-based 2017 "ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA" Guidelines for the diagnosis and treatment of elevated blood pressure in adults" recommends intensive BP control for primary and secondary stroke prevention. The guideline proposes a target BP of <130/80 mm hg [29]. The recommendations are supported by an extensive evidence document accompanying the guideline [30]. Current analysis according to 9 trials, shown a strong evidence of blood pressure regulation at <150/90 mmHg reduces the chances of stroke and 6 trials have shown strong proof that lower goals were associated with substantial decreases in stroke.

3.2. Diabetes mellitus (DM)

DM raises frequency of ischemical strokes at all ages, but the risk is greatest (risk ratio > 5) for black and white before the age of 65 [31]. Generally, patients with the ischemic stroke of DM are younger, is black more likely than non-diabetic and experience the effect of HBP (High blood pressure), MI (Myocardial infarction) and high cholesterol. DM is a risk factor that is not dependent on any other factor for stroke. An 18 studies meta-analysis involving 43899 pre-stroke subjects showed higher recurrence of stroke in people with DM in comparison to people not having DM [32].

3.3. Disorders of heart rhythm

AF (Atrial fibrillation) is a strong stroke risk factor, rising risk 5-fold independently across all ages. The percentage age of AF related strokes rises sharply from 1.5% at age 50 to 59 and 80 to 89 years of age, 23.5% [33, 34].In AF patient's anticoagulation, presence of persistent AF versus paroxysmal AF is linked to elevated risk of stroke [35, 36].

3.4. High blood cholesterol and other lipids

Elevated TC (Total cholesterol) is inversely related in multiple studies with hemorrhagic stroke. In a meta-review of 23 prospective cohort studies, 1 mmol higher TC the chance of hemorrhagic stroke was 15% lower [37]. A randomization study of lipid genetics suggested a

higher threat of large arteries ischemic stroke with increased LDL and a reduced risk of small-vessel ischemic stroke with increased HDL [38].

3.5. Smoking/Tobacco use

Current smokers have a higher threat of 2 to 4 times of stroke in analogy to non-smokers or those who have been quitting for more than 10 years [39, 40]. Smoking cigarettes is an ischemic stroke risk factor and SAH (Subarachnoid hemorrhage) [41]. The most crucial modifiable threat factor in avoiding SAH is smoking, with the highest PAR (Population attributable risk) of any SAH risk factor (38% -43%). According to a major Danish cohort study, among people suffering from AF, smoking was connected to increased risk of Ischemical stroke / arterial embolism or death after adjustment for other traditional risk factors [42]. Decreased stroke risk across sex, race, and age groups can be seen following the discontinuation of smoking[43, 44].

3.6. Physical inactivity (PA)

The ARIC (Atherosclerosis risk in communities) study after 17 years of average follow-up of, found an important trend among African Americans toward reduced incidence of stroke with increasing level of PA, a similar the trend was noted for whites in the study, though it wasn't statistically relevant. These study data informed that although the levels of activity were most protective, even modest levels of PA it seemed beneficial [45]. Physical inactivity was linked with elevated risk of stroke between individuals > 80 years of age in NOMAS (Northern Manhattan Study) [46]. In the millions of individuals researching a future analysis of the cohort of women in England and Scottish over an average of 9 years of self-reporting of any PA at baseline was connected with reduced threat of stroke and its subtypes [47].

3.7. Nutrition

Follow-up research in nursing health and health professionals showed that 1 serving increase in sugar-sweetened soda drink was linked to increased risk of 13% ischemic stroke and each 1 serving increase in low calorie or dietary soda was with a 7% increase in ischemic stroke risk and a 27% increase in hemorrhagic stroke risk [48]. A meta-analysis of > 94000 people with 34817 stroke incidents found that consuming about 5 portions of fish per week compared to eating < 1 portion per week was attached to 12% drop in stroke threat; however, these findings were not consistent across all cohort studies [49].

3.8. Family history and genetics

Ischemic stroke is an inheritable disease; stroke family history is related with risk of stroke, stroke subtypes, and carotid atherosclerosis [50]. Heritability of stroke appears to play a larger role in younger strokes. Genetic factors seem to be largely more vital and small strokes than in cryptogenic or cardiovascular strokes [51].Genetic studies established risk-related forms of genetic ischemic strokes, with distinct hereditary associations [52].

3.9. Kidney disease

A meta-analysis of 21 studies covering > 280000 patients found a 43% increased threat of incident stroke among GFR (Glomerular filtration rate) < 60 mL/min patients [53].A meta-analysis exhibited that a higher level of albuminuria poses a higher stroke risk, providing evidence of a strong connection between albuminuria and the risk of stroke, and recommended that people with high elimination of albumin through urine could result in a beneficial and more intensive reduction in vascular risk [54].

A meta-analysis showed that the incidence of strokes increased linearly and additively with a decrease in GFR and an improvement in albuminuria, suggesting that CKD (Chronic kidney disease) staging could also be a valuable diagnostic method for determining people most likely to benefit from treatments in ACR (Albumin-Creatinine ratio) [55].

3.10. Risk factor issues specific to females

Guidelines on the Stroke Prevention in females, a note to Health Professional of the USH Association / American Stroke Association. 207 Recent meta analyzes of the 32 studies have shown that females who experienced menopause were at increased risk of stroke before 45 years, as compared to females [56]. A higher risk is associated with a period of 2 days before and after 1day delivery and less than 6 weeks after delivery of ischemic stroke and ICH (Intracerebral hemorrhage) [57].

3.11. Stroke in children

Pediatric strokes are classified as either perinatal (including in utero strokes) or (later) childhood based on pathogenic variations (28 days of life). Presumed perinatal strokes are diagnosed with hemiparesis or other neurological symptoms later in infancy in children without newborn symptoms [58]. Cerebral arteriopathy, which occurs in more than half of all

cases, is the most common reason of arterial ischemic stroke in children [59, 60]. Childhood arteriopathies are heterogeneous and can be hard to differentiate when setting up a cardioembolic stroke [61].

American boys have a 25% higher risk of ischemic stroke and a 34% higher risk of ICH compared to girls, whereas a study in the United Kingdom found no sex difference in ischemic stroke in children [62]. Black children in both the United States and the United Kingdom have more than 2-fold risk of stroke compared to white children. Increased risk among black boys is not fully explained by black children [63].

Between young adult childhood survivors' stroke, 37t had a typical adjusted Rankin score, 42% had mild deficits, 8% had medium deficits, and 15% had extreme deficits [64]. Concomitant contribution of basal ganglia, cerebral cortex, and the internal capsule's posterior limb indicates a persistent hemiparesis [65]. Despite current care, at least one out of ten children wear a persistent hemiparesis [66, 67]. In a survey of 111 pediatric stroke patients admitted to a single hospital for children in the United State, the average1-year direct cost of a childhood stroke (inpatient and outpatient) was about $50000 with a total of about $1000000. More severe neurological damage associated with higher direct costs of a stroke at 1 year and lower quality of life in all domains after a childhood stroke [68].

3.12. Stroke in the young

Around 10% of all strokes in people between the ages of 18 and 50 [69]. The prevalence of 3 to 5 risk factors also increased from 2003-2004 to 2011-2012 [70]. Among males, the prevalence of 3 or more risk factors among stroke patients increased from 9% to 16% at 18 to 34 age, 19% to 35% at 35 to 44 age, 24% to 44% at 55-66 age. Among women, the occurrence of present risk aspects among patients having stroke increased from 6 to 13 per cent at the age of 18 -34, 15 to 32 per cent at the age of 25- 44% and 27-48% at age 55-65.

The first-ever stroke sex-based rate of incidence among whites aged the population of 20 to 54 was 48 in 100000. In the 2005 GCNKSS (Greater Cincinnati/Northam Kentucky stroke) study period, in comparison 128 blacks in every 100000 of the same age. The incidence rate of both races increased significantly between 1993 and 1994 [71]. In the future study, stroke patients 18 to 50 of age had a 30-day fatality rate of 4.5%. One-year mortality for 30-day patients was 1.2% for TIA (Transient ischemic attack), 2.4% for ischemic stroke, and 2.9% for ICH [72].

3.13. Stroke in older adults

Stroke patients > 85 age 17% of all patients with stroke, is more common in females in this age group than in males [73, 74]. Patients of age 65 and above are known to be at higher risk-adjusted mortality[75], have a higher disability [75], have longer hospitalizations [76], receive less evidence related care [77, 78], and a place of origin is less likely to be to their original place of residence [79, 80].

As per US NIS analyzes, the mortality rate in hospitals after stroke have declined in each age and sex group in the last decade, with the exception of males aged > 84 years [81]. Over the period from 2010 to 2050, the number of strokes in the accident is estimated with the majority, more than double rise in the elderly (age > 75 years) and minority groups [82].

4. CONCLUSION

Cerebral ischemia is a critical challenge for physicians from a treatment point of view. In this review, we presented current research findings on the mechanistic pathways in cerebral ischemia. Several described here, damaging leukocytes in the brain parenchyma can elevate ischemic damage, glutamate is engaged with the progression of ischemic cell damage, break in the bloodstream causes lactic acidosis, irritation of sodium potassium pumps, glutamate intake and cytotoxic edema, oxidative brain damage contributes to ischemic brain injury, during brain ischemia, intense oxygen and glucose hardship prompts failure of neurons to integrate adequate ATP from oxidative digestion, BBB interruption which prompts vasogenic edema and aggravation, necrotic cells become edematous and lose their cell structure by cytoskeletal breakdown, brief platelet collection leads to spillage of BBB and irregularities in vascular reactivity. Although the detailed mechanisms associated with cerebral ischemia remain to be fully revealed, we believe an understanding of the mechanistic pathways has the potential to provide a strong foundation for the exploration of new therapeutic possibilities.

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CONFLICT OF INTEREST

There is no conflict of interest.

AUTHORS' CONTRIBUTIONS

KP and SJ were responsible for the study concept and design; they systematically reviewed the literature. KP and SJ wrote the manuscript. All authors edited and approved the final version of the manuscript to be published.

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List of figures

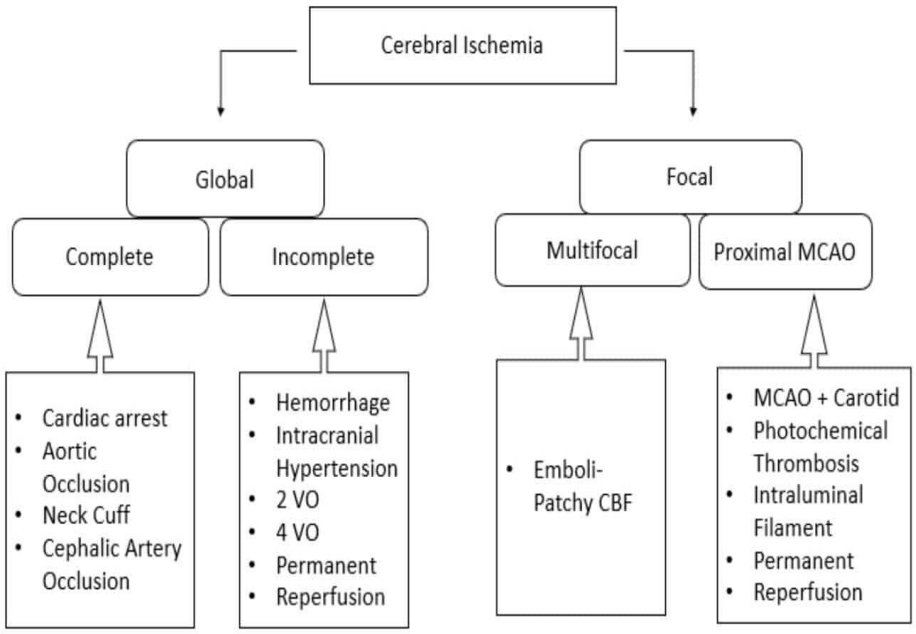

Figure.1. Models of cerebral ischemia

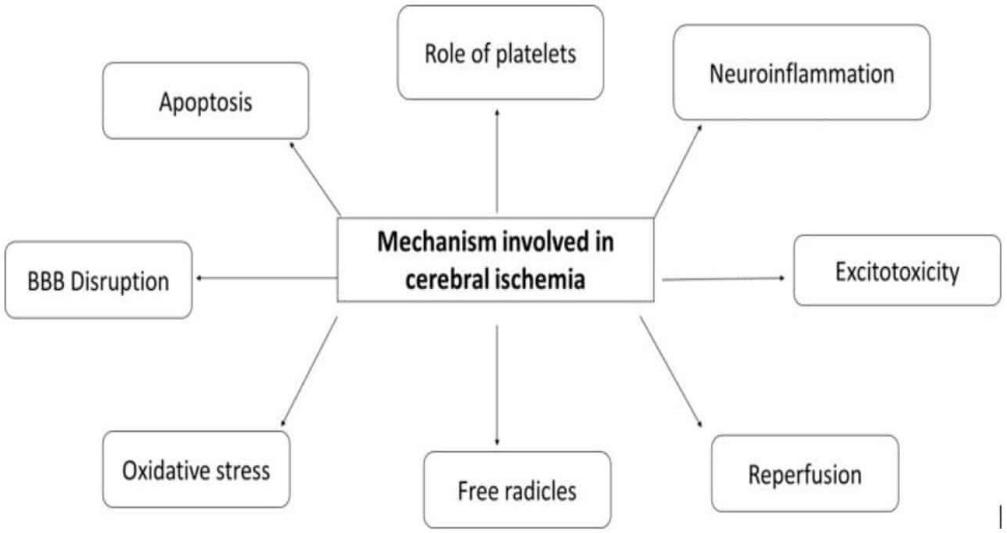

Figure.2. Mechanism involved in cerebral ischemia.

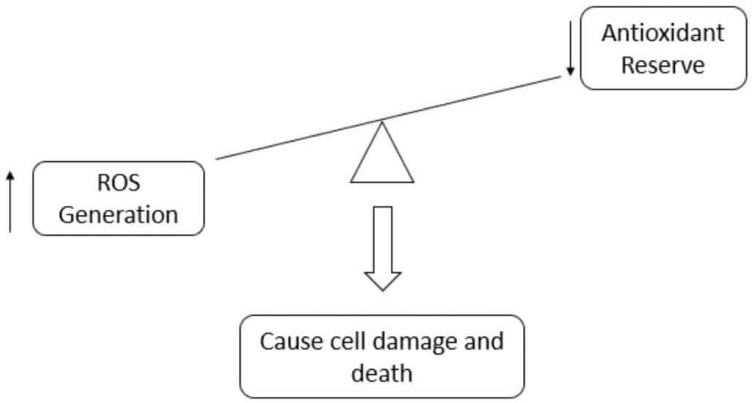

Figure.3. Mechanism of cell damage and cell death in ischemic injury

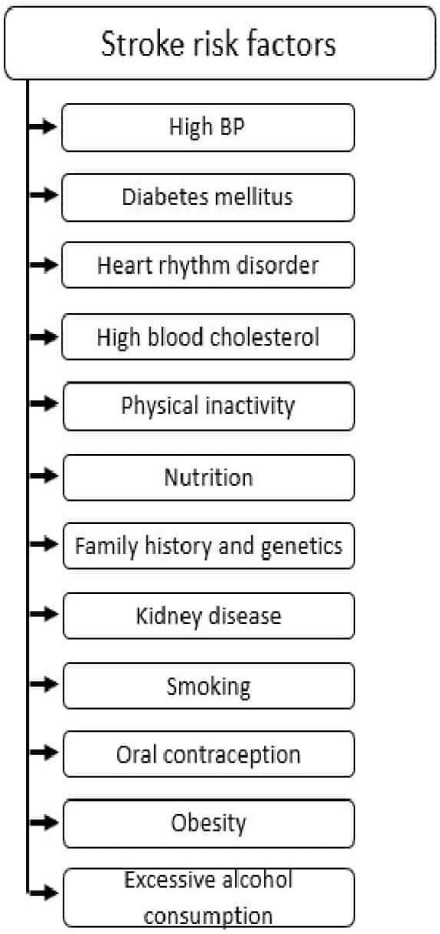

Fig. 4. Risk factor related to cerebral ischemia.