Stroke: Is a major culprit for cerebrovascular disease?
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Abstract
Stroke is an important cause of morbidity and mortality and the second leading cause of dementia worldwide. The main cause of stroke is the intermission of the blood supply to the neurons either due to ischemia or due to bursting of blood vessels. The pathophysiology of the stroke is very complex and is difficult to understand. There are various pathological conditions which provoke stroke included platelet aggregation, mitochondrial dysfunction, hyperhomocysteinemia, glutamate excitotoxicity, various genetic disorders, destruction of endothelial cell wall, atherosclerotic plaque formation, accumulation of bilirubin within the neurons, hyperfibrinogenemia, accumulation of inflammatory mediators like interleukins, chemokines, cytokines, neutrophils, leukocytes etc. results in loss of neuronal functions and neuronal death. The objective of this review is to throw light over the various pathophysiological pathways involves in the evolution of stroke.

Key-Words: Hyperhomocysteinemia, Stroke, Interleukins

Introduction
Stroke is a heterogeneous group of cerebrovascular conditions and is a sudden and devastating illness. However, many people are unaware of its widespread impact [1]. A stroke or “brain attack” occurs when a blood clot blocks the blood flow in a vessel or artery, interrupting blood flow to an area of the brain result damage of brain cells. When brain cells die during a stroke, abilities controlled by that area of the brain are lost. These include functions such as speech, movement, and memory [2, 3]. However, the World Health Origination defines a stroke as “Rapidly developing clinical signs of focal or global disturbance of cerebral function lasting more than 24 hours with no apparent cause other than a vascular origin” [4]. Moreover, Cardiovascular stroke is a broad term used to describe the syndrome in which acute vascular and brain tissue change manifests as one or more neurologic defects that last more than 24 hours, these defect results from either inadequate blood flow or hemorrhage [5]. Researchers observed that stroke is a global health problem. However, it is the second leading cause of death and fourth Leading cause of disability worldwide.

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Approximately 20 million people each year will suffer from stroke and of these 5 million will not survive. As in developed countries, stroke is the first leading cause of disability, the second leading cause of dementia [6]. It is also a predisposing factor for epilepsy, falls and depression in developed countries [7]. It can be identified from the symptoms occurs during it include: vertigo, sensory loss, facial numbness, ataxia, dysphagia, dysarthria, ophthalmoplegia, arm and leg paralysis, amnesia, color amnesia, or coma. Stroke patient’s suffers from many other complications like sleep problem, confusion, depression, incontinence, atelectasis, pneumonia and swallowing dysfunction that causes aspiration, dehydration or malnutrition. Immobility can lead to thromboembolic disease, reconditioning, sarcopenia, UTIs, pressure ulcer and contractors. Daily functions include the ability to walk, see, feel, remember, think, and speak may be decreased [8-10]. Stroke can be majorly classified into two types including ischemic stroke and hemorrhagic stroke. An ischemic stroke is that kind which includes narrowing or blocking of the blood vessels that leads to the brain's supply due to which the supply of blood to the brain is cut off [11]. The most common cause of ischemic stroke in humans is occlusion of the middle cerebral artery (MCA). It can be thrombotic, embolic, or due to systemic hypoperfusion or to venous thrombosis [12]. Hemorrhagic stroke is the one in which the blood vessels present in the brain or situated near the brain...
bursts that causes bleeding and stopping the oxygen supply to the surrounding areas of the brain [13]. Hypoxia is the major reason for hemorrhagic stroke which caused destruction of the brain tissues and vasculature due to which intracranial pressure is increased resulting in bleeding [14]. This present review article described the pathophysiology of stroke.

Material and Methods

Pathophysiology of Ischemic stroke

Role of inflammatory mediators in acute ischemic stroke: - Astrocyte and glial cells are the building blocks of nervous system. These cells act as a bridge between vessels and neurons [15]. As, the major function of these cells is to maintain the homeostasis, therefore, is a crucial mediator of inflammatory responses in case of brain injury. Cerebral ischemia evokes the inflammatory mediators such as Cytokines and chemokine. However, the chemokine and cytokines further involve the enrollment of leukocytes. Moreover, the physiological role of leukocyte involves phagocytosis and regulation of molecular events including the thrombin formation which is further responsible for the cellular changes such as chemotaxis, proliferation and more pronounced cytokine and chemokine release [16, 17]. However, the most pertinent subfamilies of chemokine that would act as a booster in cerebral ischemia are CC and CXC. These two will be the reason for the assessment of neutrophil and monocyte which act as phagocytic cells [18]. Endothelial cells secrete the cell adhesion molecule in response to the inflammatory changes. Now, these cell adhesion molecules further promote the glial cells to secrete chemokine after ischemic stroke [19]. However, chemokine already reside in the brain at very low levels, which includes CX3CL1 (Fractalkine) present in neurons and CXCL12 resides in astrocytes. The major functions of chemokine in the brain are to maintain the homeostasis [20]. After the brain Injury, the level of chemokine goes on increasing which recruits all the inflammatory mediators like TNF – α, IL-1, IL-6 resulting in the activation of ischemic cascade [21]. Moreover, CCL2, CCL5 and CXCL8 are chemokine that will participate in the pathophysiology of stroke [22]. However, CD40 receptors are also responsible for the activation of proinflammatory mediators. The over activation of the CD40 receptors caused the recruitment of cytokines and adhesion molecules (Fig 1) [23].

Role of homocysteine in stroke: - Homocysteine is the amino acid that carries Sulphydryl group. The demethylation of methionine results in the production of Homocysteine [24]. However, homocysteine is responsible for the various changes include lipid peroxidation, free radical formation, and Inflammation which further leads to atherosclerosis [25, 26]. The sulphydryl group is the culprit for all the damages occurred by homocysteine. Sulphydryl group is responsible for the autoxidation of homocysteine and thiolactone formation that would further lead to atherosclerotic plaque formation [27]. However, hyperhomocysteinemia would lead to the production of peroxynitrite. Moreover, this peroxynitrite stimulates Poly (ADP-ribose) Polymerase (PARP). As PARP stimulates the uncoupling of NO synthase leads the nitration of protein tyrosine residue results in vascular damage and arise oxidative stress. This would result in the imbalance between vasoconstrictor and vasodilator factors [28]. Hyperhomocysteinemia restricts the growth of endothelial cells, decreases the expression of adhesion molecules and leads to the formation of low density lipids (LDL). It also modifies coagulation and fibrinolysis system [29].

Role of ATP and glutamate in stroke: - Brain is the organ which consumes high energy level of the body so it needs high glucose and oxygen. Any restriction in the flow of blood causes brain injury. However, cerebral ischemia leads to ATP depletion in the neurons, glial cells and small vessels which further results in lactic acid accumulation. The accumulated lactic acid provokes the formation of free radicals and increases the release of glutamate [30]. Moreover, reduced levels of ATP inhibit the Na⁺/K⁺-ATPase leads to depolarization of neurons and astrocytes. However, on hypoxia astrocyte activates the glycolytic activity permitting the continued uptake of glutamate from the synaptic cleft to the penumbra. [31]. The increased level of glutamate further activates the glutamate N-methyl-d-aspartate (NMDA) receptors. The over activation of glutamate receptors results in excitotoxicity is the condition in which cell dies due to the toxic actions of excitatory amino acids [32, 33]. However, glutamate involved in a number of pathological changes includes impairment of calcium buffering, activation of mitochondrial permeability transition pore and free radical generation [34]. Therefore, excessive release of glutamate causes mitochondrial dysfunction, which further causes the assessment of apoptosis- caspase cascade leads to cell death (Fig. 2) [35-36].

Role of endothelium in stroke: - The major role of cerebral endothelium is to regulate hemostasis and the formation of blood brain barrier (BBB) [37]. To achieve homeostasis, blood flow brings antithrombotic and anti-inflammatory agent to endothelium, which includes thrombomodulin-protein-C-protein S system, heparin like molecules, tissue factor pathway

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inhibitors, tissue plasminogen activator (t-PA), prostacyclin, adenosine diphosphatase, deminase enzyme which removes C-terminal tryptophan from endothelin-1. However, at the time of injury endothelium undergoes considerable changes, i.e. activation of antithrombotic factors and anti-inflammatory mediators. Therefore, leukocyte activates the adenosine receptors [38]. The other changes include activation of platelet activating factors such as factor VIII/von willebrand factor, thromoxane A2 [39] and the three isoforms of endothelin i.e. ET-1, ET-2, ET-3 which further results in the accumulation of various inflammatory mediators, vasoconstriction and brain hemorrhage [40, 41]. Moreover, decreases the matrix ligands like Iminin-1, laminin-5, collagen-1 and fibronectin from the basal lamina results in middle cerebral artery occlusion that further escalate neuronal injury. As, Ischemic insult causes swelling of astrocytes, decreases the consistency of cytoplasmic density and swelling of endothelium therefore, brings middle cerebral artery occlusion [42].

**Role of hepatic encephalopathy in stroke:**- Hepatic Encephalopathy causes the accumulation of toxic metabolites in the body like ammonia, urea. Cirrhosis is the condition that causes severe hepatic damage and destruction of hepatocytes [43]. However, intestine absorbed toxic metabolites, but the destructed liver is unable to excrete that from the body which further transported to brain through blood. There it increases the permeability of blood brain barrier. Moreover, auto-regulation of cerebral blood flow is impaired in case of hepatic encephalopathy [44], which results in decreasing the metabolism of oxygen in the brain due to which brain suffers from hypoxia. However, it may also result in decreasing the velocity of blood to middle cerebral artery that provokes cerebral ischemia [45].

**Role of cardiac embolism in stroke:**- Destruction of cardiac muscles causes the condition called as cardiac dysfunction, which further results in improper functioning of cardiac pumps. Therefore, results in the restriction of the flow of blood due to which thrombin red clot is formed. However, the thrombus fragments are accomplished in the systemic arterial circulation [46]. As, the heart supplies 20% of blood to the brain, therefore, the clot embolized to an intracranial artery. This results in the occlusion of intracranial artery. Moreover, blood applies force to restore the supply of blood to the brain, which further causes dispersion of clot and formed embolus at the different sites of artery [47].

**Role of toll like receptors (TLRs) in stroke:** - TLRs are the superfamily that mediates innate immune responses. It is Class 1 Membrane Protein which comprised of ectodomains, transmembrane and intracellular TLR domains. When the ligands bind to TLR that brings conformational changes in the receptor [48]. These changes enrolled the intracellular adaptor proteins such as MyD88, TRIF, TIRAP or TRAM all of it causes the activation of NF-κB (Nuclear Factor Kappa B). The ligands which activate the receptor include heme, fibrinogen, high mobility group protein B1, hyaluronan, oxidized low density lipoprotein, amyloid β [49]. TLRs mediate its effect by the activation of two signaling pathways, which is activated by the adaptor protein i.e. MyD88 and TRIF. The activation of MyD88 regulates the action of pro-inflammatory cytokine genes and activation of NF-κB. However, the activation of TRIF includes TLR3 and TLR4 mediated the pathway, which further include the enrollment of IRF-3 results in stimulation of IFN-β [50]. Therefore, IFN-β involves the recruitment of macrophage infiltration. However, the activation of NF-κB recruits TLR2 and TLR4 which evoke brain ischemia. TLR4 pathway further leads to the activation of AP-1 (activating protein 1) which is dimeric protein. However, this dimeric protein consists of members of Jun, FOS and α-Feroprotein. Furthermore, MMPs includes MMP2, MMP3, MMP9, MMP12 and Protease activation enrolled t-PA [51]. However, AP-1 also includes the assessment of mitogen activated protein kinase like c-Jun-N-terminal kinase (JNK), p38, extracellular signal regulated kinases (ERK) [52].

**Role of monogenic diseases in stroke:** - It had been observed that about 5% of stroke cases are reported due to the mutation in the genes. Gene-gene interaction or gene-environment interaction being the major reason for this mutation. These genetic factors modify the target organs and therefore, become the risk factors that are responsible for the stroke [53]. Following are the some mutational changes that are responsible for the stroke

**Familial Hemiplegic Migraine:** - The mutation of CACNAIA gene is responsible for childhood stroke [54]. However, CACNAIA gene encoding Alpha 1A sub-unit of Voltage Gated Calcium Channels [55].

**Cerebral Autosomal Dominant (CADASIL) Arteriopathy with subcortical infarct and Leukoencephalopathy:** - Mutation of NOTCH3 gene is the major reason for the evolution of this disease which further evokes stroke with the passage of time [56]. However, this is the disease of cerebral small vessels, which further causes the vascular cognitive impairment. Moreover, Basal Ganglia and Temporal Lobe suffered from ischemia due to this disease and developed ischemic lesions in these areas [57].
Fabry disease: It is X-linked congenital lysosomal storage disorder [58]. However, impairment in α-Galatosidase that causes the accumulation of glycosphigolipids in the vascular endothelial cells, kidneys, heart, neurons which further results in tissue damage [59].

Role of renin angiotensin aldosterone system in stroke: Angiotensin converting enzyme (ACE) is a membrane bound enzyme which is very important for the conversion of angiotensinogen to angiotensin I (ANG I) and angiotensin II (ANG II). However, ANG I and ANG II play the crucial role in the development of hypertension, atherosclerosis, and cardiovascular diseases [60]. ACE gene is located on chromosome 17q23 and also contains 26 exons. However, 287 bp located in intron 16 at ACE gene is responsible for the polymorphism by addition and deletion. Furthermore, this polymorphism leads to ischemia, which further developed infarction [61].

Role of sickle cell anemia and stroke: Sickle cell anemia is the genetic disorder which plays the heterogeneous role in the development of stroke. Sickle red blood cells stick to the vascular endothelium, which creates hydrostatic pressure and shear stress [62]. However, these blood cells first of all bind to thrombospondin, VCAM (vascular adhesion molecule), P-Selectin which further creates the interaction between sickle red blood cells and vascular endothelium results in vascular occlusion [63]. Moreover, sickle cell anemia leads to an infraction in childhood and hemorrhage in adults. Furthermore, these cells also activate the accumulation of NF-κB, endothelin, and leukocytes that further worsen the occlusion results in a stroke [64].

Role of ischemic effect in stroke: Decrease in the blood flow toward the brain due to many reasons like rupturing of arterioles and parenchymal hemorrhage, which abruptly decreases the blood pressure or intracerebral hemorrhage that bring a reduction in the perihenatomal blood flow [65]. However, the perihenatomal blood reduction becomes the major cause, for the accumulation of proteins within the neurons. The proteins such as: heat shock protein 105, L-lactate dehydrogenase A, Peroxisiredoxin 1 (PRDX1), glutathione-S-transferase P, α-enolase, pyruvate dehydrogenase E1, fructose-bisphosphate aldolase C, 6-phospohfructo kinase type C, catalase, lactoglyluthione lyase, cytoplasmic enzymes of glycolysis [66]. Moreover, the ischemic condition of neurons leads to the reduction of enolase level caused hypoxia [67].

Role of septin-5 protein, synaptojanin-1 protein and dynamic related protein-1 (DRP-1) in stroke: Septin 5 proteins are localized in the pre-synaptic terminal that holds negative effect on the release of neurotransmitters. It had been observed that social isolation brings the stressful conditions due to which septin- protein level decreased within the stratum which further results in ischemia of the human brain [68]. Moreover, DRP-1 is important for the outgrowth of axons by binding with the calcium channels as well as it also helps in the formation of mitochondrial outer membrane. Mutation or upregulation of DRP-1 leads to the fragmentation of mitochondria, further results in evolution of apoptosis and cell death [69, 70]. However, synaptojanin-1 protein also called phosphoinositide phosphate is distributed in the nerve terminals. Its major function is the maintenance of the amount of phosphoinositol-4, 5-biphosphate within the synaptic membrane. However, the increase in its level during ischemia causes destruction of synaptic membrane [71].

Role of hyperbilirubinemia in stroke: The byproduct of heme metabolism is bilirubin. However, when elevated level of bilirubin is concentrated within the neurons, it produced the toxic substances like urea, ammonia in the neurons which further results in the production of oxidative stress. Moreover, increased concentration of bilirubin also caused the aggregation of halogenated hydrocarbon which acts as mediator of oxidative stress [72].

Role of microRNA (miRNA) in stroke: It is endogenous small non-coding regulatory RNA molecules. It damages the messenger RNA (mRNA) through binding with their coding targets. It plays a very important role in the pathogenesis of stroke. However, miRNA shows functions like neural cell survival, impaired regulation of neurovascular integrity, stroke mediated inflammation [73]. The miRNA that participated in the evolution of stroke includes miR-124, miR-9, miR-219, miR132. These miRNA modifies the blood brain barrier by accumulating cytokines and thus causes the breakdown of blood brain barrier [74]. Moreover, miRNA involved in endothelial functions, vascular functions, erythropoiesis, angiogenesis, neural functions, hypoxia. However, circulating miRNA is the end product of microvesicle secretion which is involved in RNA-binding Agronature (Ago) proteins [75]. Necrotic cells secreted Ago proteins into the systemic circulation from the cytoplasm of the cell through destruction of cellular membranes. Therefore, it caused middle cerebral artery occlusion. In case of autoimmune encephalomyelitis, the plasma concentration of miRNA-124 is increased and miRNA-9 is decreased, thus facilitates the neuroinflammation during the stroke [76].
Role of lipoprotein associated phospholipase A2 (Lp-PLA2) in stroke:- Lp-PLA2 is a calcium independent phospholipase and is also called as Platelet-activating factor acetyl hydrolase (PAF-AH). However, it is involved in the cleavage of oxidized Phosphatidylcholine and thus formed lysophosphatidyl choline (lyso-PC) and oxidized non-esterified acids [77]. Therefore, it participates in the activation of proinflammatory mediators. Moreover, Lp-PLA2 is encoded by PLA2G7 gene, which is localized on chromosome 6p21-p12. However, the polymorphism of V2797 which is present in exon 9 of PLA2G7 gene associated with the development of coronary diseases, stroke, and carotid atherosclerosis [78].

Role of stromelysin-1 in stroke:- It is a matrix metalloproteinase that further regulate extracellular matrix in case of tissue injury. Therefore, it gives rise to the growth of atherosclerotic plaque. In its gene sequence the promoter of the gene contains 600bp which have 6 adenosine (6A) whereas the other genes contain only 5 Adenosine (5A). However, 5A allele shows more pronounced activity than that of 6A allele. Therefore, 6A allele contains lower levels of stromelysin in arterial walls results in the accumulation of matrix within the cells, which further increases the thickness of carotid artery walls [79].

Role of hyperfibrinogenemia in stroke: - It is the condition of elevated plasma fibrinogen levels. Hyperfibrinogenemia leads to the impairment of the blood coagulation system which increases the blood viscosity and decreases the flow of blood. Therefore, it promotes the platelet aggregation and adhesion to the endothelial cells [80]. However, fibrinogen is a dimeric glycoprotein contains 3 pairs of polypeptide chains, i.e. two strands of Aα, Bβ and γ. Moreover, these six polypeptide chains construct Hexamer (AαBβγ) 3. Furthermore, these polypeptide chains, i.e. Aα, Bβ and γ are encoded by the different genes alpha fibrinogen gene (FGA), beta fibrinogen gene (FGB), gamma fibrinogen gene (FGG) respectively. However, single nucleotide polymorphism (SNPs) of Bβ influences plasma fibrinogen levels, therefore, Bβ limits the production and maturation of fibrinogen. Moreover, SNPs in FGB at -148C/T located in FGB promoter gene observed that person with T allele have higher fibrinogen level than C allele [81].

Conclusion
As stroke is a global health problem, therefore, it is being very important to know about the pathological pathways, further it helps in the treatment of stroke. Ischemia causes the accumulation of inflammatory mediator’s results in phagocytosis, thrombin formation and oedema. Moreover, the deficiency of folic acid and vitamin B12 leads to hyperhomocysteinemia which further results in lipid peroxidation, free radical formation, and endothelial dysfunction. However, endothelial dysfunction causes imbalance between vasodilators and vasoconstrictors agents. Excessive secretion of glutamate due to depletion of ATP causes over activation of NMDA glutamate receptor further results in mitochondrial destruction. Therefore, mitochondria start releasing caspase-3, -7 and 9 which results in apoptotic cell death. Sometimes, the genetic disorders also provoke a stroke like familial hemiplegic migraine, cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy, fabry disease, sickle cell anemia. Moreover, the mutation of ACE gene also brings the condition which favors the evolution of stroke. However, activation of TLR with the specific ligands causes the activation of TLR-2 and TLR-4. Moreover, accumulation of bilirubin within the neurons results in the production of toxic substances and oxidative stress. MicroRNA leads to the necrotic cell death, miR-124 and miR-9 are the major microRNA which is involved in the pathogenesis of stroke. This article has compiled the pathophysiologial roles of various types of diseases, mediators, gene and proteins in stroke.

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Fig. 1: The role of inflammatory mediators resulting leukocyte migration.
Fig. 2: Figure indicates the over-activation of NMDA glutamate receptors lead to apoptotic cell death

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