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BRAIN STROKE - AN OVERVIEW OF THEIR CAUSATIVE FACTORS AND CURRENT TREATMENT STRATEGIES

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ABSTRACT

Stroke is a disease that occurs when the inventory of blood to the brain is either blocked or ruptured. At the point when this occurs, the cerebrum fails to get enough oxygen or supplements, that leads to the death of the brain cells.It is one of the main source for causing high mortality and disability. It has been characterized either as Ischemic stroke or Haemorrhagic stroke. The most common risk factors are Hypertension, Atrial fibrillation, Heart failure, smoking, liquor utilization, over weight and hypercholesterolemia. Different pharmacological agents are used for the treatment of stroke either through intruding on the sub-atomic pathways prompting neuronal death or improving neuronal endurance and recovery. Apart from recombinant tissue plasminogen activator (rtPA), there are few agents that could treat the stroke, have been prevailing in clinical testing. Early revascularization is as of now the most settled treatment for acute ischemic stroke that adequately improves clinical results. The current research in the medical field is focusing on creating the neuroprotective agents for stroke treatment, and novel sub-atomic focuses for neuroprotection and neuro restoration and this has been found to anticipate the clinical advantages. In this review the risk factors, basic pharmacological treatments and clinical manifestation for ischemic stroke are discussed.

Keywords: Brain, Stroke, Haemorrhage, Ischemia, Tissue Plasminogen Activator Pharmacological agents, Neuroprotection

1. INTRODUCTION

Stroke is a disease that causes wrecking neurological deficiencies and is the significant reason for death around the world. Stroke is a term used to describe an abrupt onset of focal neurologic deficit that lasts at least 24 hours and is presumed to be of vascular origin.Stroke can be either ischemic stroke or haemorrhagic stroke in origin. Transient ischemic attacks are focal ischemic neurologic deficits lasting less than 24 hours and usually less than 30 minutes.It occurs when a cerebral vein is blocked (ischemic stroke) or is ruptured (haemorrhagic stroke) **[1]**. In most of the cases 87% of ischemic stroke causes neuronal death, aggravation, and damage of the neurovascular unit, which lead to serious neurological adverse effects.Quick reclamation of the cerebral blood stream is the essential objective of ischemic stroke treatment just as the pre-imperative to neuroprotective treatments.The world-wide assessment shows that 25% of both men and women who are above 25 years gets easily affected by stroke, with the danger of ischaemic stroke being about 18% and about 8% for haemorrhage **[2]**.

The general analysis of stroke patients revealed that about 80% of strokes are cerebral ischaemia, and 20% are cerebral haemorrhage. Most of cerebral strokes are ischemic and it occurs because of the obstruction in the cerebral vein by a thrombus or an embolism and loss of tissue perfused by that vessel. when compared to the last 10-20 years, now the stroke care units has improved a lotand constrained advances are made in the treatment to balance the injurious impacts of ischemic stroke. Intravenous thrombolysis through recombinant tissue plasminogen activator (rtPA) is the main pharmacological treatment for acute ischemic stroke recommended by US Food and Drug Administration (USFDA). Because of the thin therapeutic window (<4.5h) and reperfusion damage instigated by rtPA, just 5% of patients at present are getting cured by rtPA treatment and within the 3 hours of symptom onset it should be given **[3, 4]**. The aim of this review is to provide a detailed explanation about the causes of the brain stroke, pharmacological treatment and its clinical manifestation.

2. RISK FACTORS

The existence of risk components is critical for making preventive methodologies to diminish stroke occurrence. The most common risk factors of stroke are hypertension, smoking, liquor utilization, low physical movement, overweight and hypercholesterolemia. While, air contamination, hereditary factors and workplace are slightly found to advance the stroke event. So risk factors of stroke become an increasingly and complex elements. As indicated by the condition of the body, the risk factors can be characterized in to two classifications namely internal risk factors (hypertension, hypercholesterolemia, hereditary components) and external risk factors (smoking, liquor utilization, air contamination) **[5, 6]**.

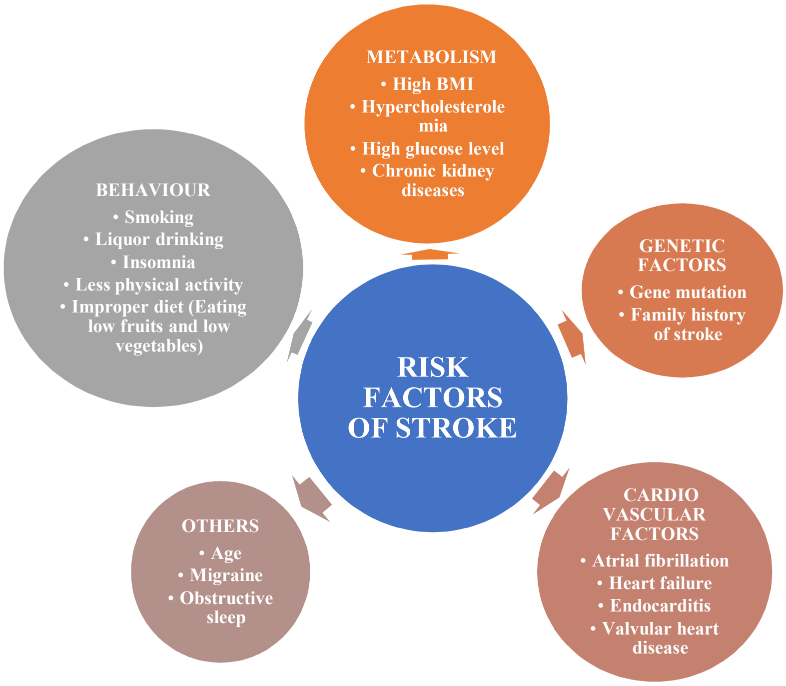

Figure 1: Different Causes of stroke

2.1. Risk factors in haemorrhagic stroke

Haemorrhagic stroke are of two types namely intracerebral haemorrhage and subarachnoid haemorrhage, however it can cause about 40% of all stroke deaths. Multiple risk factors like, hypertension, smoking, high liquor consumption and renal dysfunction, gradually increases the occurrence of haemorrhagic stroke. Intracerebral haemorrhage is the main type of haemorrhagic stroke and its autonomous risk factors includes substantial liquor drinking, hypertension and anticoagulant treatment. While hypertension, smoking, cocaine usage increases the rate of subarachnoid haemorrhage **[7, 8]**.

2.2 Risk factors in ischaemic stroke

Ischaemic stroke is the most widely recognized type of stroke and can be characterized into:

Large vessel occlusion; Cardio embolism; Small vessel occlusion; Stroke of other determined cause; Stroke of undetermined cause.

Hypertension, smoking, high liquor consumption, atrial fibrillation and diabetes are the risk factors that gradually increases the occurrence of ischaemic stroke. As a result, from many countries there are many factors that contribute to the ischaemic stroke, while, smoking, hypertension and liquor intake seems to be more progressively related with haemorrhagic stroke. In cohort studies, high cholesterol or high density lipoprotein cholesterol proportion diminishes the intracerebral haemorrhage rates however there is increased ischaemic incidence **[9, 10]**.

3. CHALLENGES AND TREATMENT STRATEGIES

Early revascularization is the most established treatment for acute ischemic stroke that adequately improves the clinical results. There are two fundamental ways to accomplish the revascularization they are thrombolysis utilizing intravenous (IV) rtPA and mechanical thrombectomy (MT) both have a restricted therapeutic window. Since mid-1990s there has been no effective interpretation of pre-clinical tested neuroprotectants in the clinical use. In clinical trials the failure of neuroprotectants can be clarified by the way that stroke includes numerous mechanisms and it influences the heterogeneous populations **[11]**. The traditional neuroprotection methodologies are constrained to a single mechanism, for example, reducing the glutamate, calcium ions, ROS, and inflammatory factors or replenishing neurotrophins. The results shows that the tested medications are not enough to inhibit the complex pathophysiological cascades in stroke patients. In the sub-acute and chronic phases of stroke, other than post-stroke recovery, which re-establishes neurological function and improve patients personal satisfaction, cell-based treatment has demonstrated extraordinary possibilities **[12]**.

Cell-based treatment has been established in animal models, broadly explored in clinical settings, and indicated that there is an advantage in promoting endogenous angiogenesis and neurogenesis. With the improvement of gene technology, non-coding RNAs serve as direct targets for neuroprotection in experimental stroke. The non-coding RNAs such as small inhibitory RNA (siRNA), microRNA (miRNA), piwi-interacting RNA (piRNA), and long non-coding RNA (lncRNA), which are all expected to regulate gene function at the transcriptional and post-transcriptional level **[13]**.

3.1 Revascularization Treatment

Various randomized controlled trials have revealed that effective revascularization is advantageous for the clinical result of acute ischemic stroke. IV rtPA is right now the first-line treatment for revascularization, while substitutive or adjunctive treatments are applied either alone or in combination with rtPA to get beneficial outcomes.

3.1.1 Thrombolytic agents

The National Institute of Neurological Disorders and Stroke (NINDS) stroke trial affirmed the advantage of administering IV rtPA within 3 h of symptom onset **[14]**. In The European Cooperative Acute Stroke Study III (ECASS-III) trial, IV rtPA demonstrated that the patients treated somewhere in the range of 3 and 4.5 h after the onset of stroke **[15]**. A few novel thrombolytic agents have been developed and are conceivably much ideal than alteplase. The tenecteplase has a more binding affinity for fibrin, higher protection from inactivation by Plasminogen Activator Inhibitor- I (PAI-1), and longer half-life **[16]**. In any case, in a trial of 1,100 subjects, tenecteplase at a dose of 0.4 mg/kg neglected to exhibit prevalence and had a safety and efficacy profile like that of alteplase **[17]**. The extraction of saliva from vampire bats is known as Desmoteplase. This is profoundly fibrin-specific and in phase III clinical trials vowed to extend out the therapeutic window up to 9 h from indication onset **[18]**.

3.1.2 Therapy after arterial recanalization

The essential objective of stroke treatment is to expel the impeding blood clot and to recanalize the artery in the short time. Over half of patients with effective rtPA thrombolysis or endovascular treatment have a troublesome result, which attributes to the "arterial reocclusion," "no-reflow phenomenon," and "haemorrhagic transmission" **[19]**. "Arterial reocclusion" is defined as a consequent occlusion of a target vessel after the beginning of recanalization. 13 to 34% of patients who were treated with rtPA have experienced an early clinical re-disintegration after thrombolysis **[20, 21]**.

As the mechanism prompting arterial reocclusion is not clear, so more studies are necessary to examine the initiation of the coagulation cascade and the penetration of pro-coagulation factors. The factors such as Thrombin-activatable fibrinolysis inhibitor (TAFI) and Plasminogen Activator Inhibitor-1 (PAI-1). It was found that the administration of low-dose intra-arterial tirofiban prevents the occlusion which is successful and safe **[22]**. No-reflow is characterized as a failure of microcirculatory reperfusion in spite of clump evacuation. The studies revealed that after effective intravenous thrombolysis, nearly half of the capillaries remains to be constrained in a mouse model of stroke **[23]**. There are some factors that contributes to no-reflow during reperfusion that involves: the impairment of vascular patency after stroke and narrowing of the microvascular lumen caused by the swollen astrocyte end feet and endothelial cells. The reduction in the microvascular clogging by hindering fibrin or platelets and leukocyte adherence or vascular inflammation re-establishes the microcirculation, decreases no-reflow, and improves stroke result in animal models **[24]**.

The various examinations have been done on this issue, yet there is no specific treatments for targeting no-reflow after stroke. It was found that by maintaining micro vascular integrity, Cilostazol may prevent no-reflow and haemorrhagic transformation **[25]**. Likewise, Pioglitazone lessens no-reflow in micro vessels in a middle cerebral artery occlusion (MCAO) rat model **[26]**. Besides, adhesion molecule blocking antibodies that restrain leukocyte adhesion, for example, P-selectin, E-selectin, Intercellular Adhesion Molecule-1 (ICAM-1) and it also prevents the no-reflow and improved rtPA-initiated reperfusion in post-ischemic cerebral mouse brain **[27,28]**. But none of these systems have been assessed in clinical testing due to the troubles in evaluating microvascular reperfusion in stroke patients.

3.1.3 Non-recanalization and Recanalization patients: Routine Therapy

For stroke patients who will get IV alteplase treatment, blood pressure (BP) ought to be brought down to <185/110 mmHg. The stability of BP have to be controlled before the beginning of IV alteplase **[29,30]**. The level of the BP should be maintained at <180/105 mm Hg at least for the initial 24 hours after IV alteplase treatment. For patients who experience mechanical thrombectomy with effective reperfusion, it is sensible to maintain BP ≤180/105 mm Hg during the process and after 24 hours it prevents the hyper perfusion disorder **[31, 32, 33]**.

The patients with BP <220/120 mm Hg who doesn’t get IV alteplase or endovascular therapy (EVT) and don't have a concurrent condition requiring acute antihypertensive treatment, starting or reinitiating treatment of hypertension within the initial 48 to 72 hours after an acute ischemic stroke isn't successful in preventing death or dependency. Administration of aspirin is prescribed in patients with acute ischemic stroke within the 24 to 48 hours of onset of the disease. For those patients who were treated with IV alteplase, aspirin administration is delayed till 24 hours later **[34, 35]**.

3.2 Neuroprotective Targets and Advances in Stroke Treatment

Neuroprotective strategy is characterized as the interference with the neuronal death falls by obstructing the signalling pathways and limiting the pathological procedures following stroke. Despite the fact that neuroprotection in stroke treatment has neglected to translate from preclinical discoveries into clinical practice, it is generally accepted that hindering stroke-induced pathophysiological cascades can help and extend the therapeutic window for recanalization and improve clinical results **[36]**.

3.2.1. Excitotoxicity

There are various investigations that have been demonstrated in the past, for proving the glutamate-mediated excitotoxicity plays a significant role in the pathogenesis of stroke. Ionotropic (iGluRs) and metabotropic (mGluRs) glutamate receptors are communicated in the central nervous system (CNS) **[37]**. iGluRs incorporate NMDAR, KAR, and AMPAR. The traditional NMDAR is a hetero tetramer made out of two NR1subunits and two NR2 subunits. NR2 subunits have more of an administrative and refining role in the NMDAR function. Following stroke, a lot of glutamate is released to stimulate receptors (mainly NMDARs), inciting ion imbalance (basically calcium) in neurons, which causes a progression of signalling falls, at long last inciting neuronal death notwithstanding the dual role of NMDAR in cell death and endurance **[38]**. Techniques focusing on excitotoxicity have been demonstrated proficient in experimental research. These methodologies includes the inhibition of glutamate discharge, up-regulating the glutamate up take system and antagonizing glutamate receptors **[39]**.

3.2.2. Reactive oxygen/nitrogen species (ROS/RNS)

The condition where the production of ROS/RNS surpasses the body's anti-oxidative capacity to check the damaging impacts of ROS/RNS is known as Oxidative stress **[40]**. The brain is susceptible to oxidative stress due to its rich substance of unsaturated lipids, moderately low endogenous antioxidant capacity, high oxygen utilization, abnormal amounts of iron that acts as pro-oxidants under obsessive conditions, and reactions including dopamine and glutamate oxidation **[41, 42]**. The factors that induces Oxidative stress are lipid peroxidation, protein denaturation, enzyme inactivation, mitochondrial and DNA damage, intracellular Ca^{2+} over-load, cytoskeletal structure damage and exhaustion of antioxidant reserves, and has been affirmed as a major component of brain damage following stroke. Consequently, the balance of oxidative and nitrosative species has been proposed as a potential therapeutic technique in restricting the extension of the ischemic lesion **[43]**. The mechanisms of free radical damage, utilizing free radical scavengers to guard oxidative stress is a crucial bearing for drug development. As of now, known free radical scavengers can be separated into two classifications:

- Classical radical scavengers (ebselen, edaravone, and so on.)
- Non-classical radical scavengers (Erythropoietin (EPO), melatonin etc.)

Until now, four compounds with classical free radical scavenging activities (tirilazad, ebselen, edaravone) or free radical trapping properties (NXY-059) have been evaluated in experimental models of stroke and assessed clinically as neuroprotective agents. The hormone that controls the ordinary circadian rhythm in mammals, and stroke patients is known as melatonin. It shows disrupted melatonin discharge in the night time.Melatonin has the anti-oxidative effects by up-controlling the anti-oxidant enzymes as well as increasing their movement and has been utilized as an antioxidant for the treatment of stroke **[44,45]**. The neuroprotective impacts of melatonin were affirmed in haemorrhagic stroke, ischemic stroke, and neonatal hypoxic-ischemic encephalopathy, and various mechanisms have been proposed other than its antioxidative impact (for instance, anti-apoptosis, anti-inflammation, calcium regulation, inhibition of excitotoxicity, and regulation of BBB integrity) **[46, 47]**. Additionally, the combination of melatonin with other different medicines accomplished better efficiency. Furthermore, some altered melatonin subordinates (Neu-P11, Molecules 5h, and ITH12674) have been designed, synthesised, and biologically evaluated. But progressively more clinical testing's are required to affirm their neuroprotective impact in stroke **[48]**.

4. CONCLUSION

Stroke causes very serious medical issues, and creating a useful treatment presently remains a major challenge. Both internal and external risk elements are significant for stroke prevention. The deep understanding about each risk factor clearly explains the specific guidance in practice. The risk factors are not completely perceived and understood nowadays, which should be further enquired about to make them progressively deliberate and precise. Apart from rtPA, some pharmacological agents have demonstrated that it is effective in clinical use. In the previous decade, much progress has been made clarifying the atomic signalling pathways and gene expression profiles underlying the pathophysiology of stroke, which provides the new therapeutic targets for stroke intervention.

Many efforts have been made to develop novel pharmacological agents and it promotes their translation. Progressively neuroprotective agents are developed in preclinical stages, the number of clinical testing's on pharmacological interventions for acute stroke has been increasing. Minocycline and edaravone have been confirmed to improve the neurological results in patients with acute ischemic stroke, which gives the translational investigations of neuroprotectants. Indeed, as progressively neuroprotective agents are developed in preclinical stages, the number of clinical trials on pharmacological medications for acute stroke has been increasing. Compared to the past decades the stroke therapy has been improved a lot but still more has to be studied in the pharmacology of brain stroke.

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