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A REVIEW ON BRAIN ATTACK

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ABSTRACT

Knowledge of stroke and the process of recovery after stroke have developed enormously in the late 20th century and early 21st century. It was not until the year 1620 that Johan Wepfer, by studying the brain of a pig, came up with the theory that stroke was caused by an interruption of the flow of blood to the brain. This was an important breakthrough, but once the cause of strokes was known, the question became how to treat patients with stroke. The primary goals of stroke management are to reduce brain injury and promote maximum patient recovery. When available, patients are admitted to an acute stroke unit for treatment. These units specialize in providing medical and surgical care aimed at stabilizing the patient's medical status. Standardized assessments are also performed to aid in the development of an appropriate care plan. Current research suggests that stroke units may be effective in reducing in-hospital fatality rates and the length of hospital stays. Once a patient is medically stable, the focus of their recovery shifts to rehabilitation. Some patients are transferred to in-patient rehabilitation programs, while others may be referred to out-patient services or home-based care. In-patient programs are usually facilitated by an interdisciplinary team that may include a physician, nurse, physical therapist, occupational therapist, speech and language pathologist, psychologist, and recreation therapist. The patient and their family/caregivers also play an integral role on this team. The primary goals of this review recovery from stroke include preventing secondary health complications, minimizing impairments, and achieving functional goals that promote independence in activities of daily living. In the later phases of stroke recovery, patients are encouraged to participate in secondary prevention programs for stroke.

Keywords: Stroke, Symptoms, Pathophysiology, Treatment.

INTRODUCTION

A stroke or "brain attack" occurs when a blood clot blocks the blood flow in a vessel or artery or when a blood vessel breaks, interrupting blood flow to an area of the brain. When either of these things happens, brain cells begin to die. 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. The specific abilities lost or affected depend on the location of the stroke and on its severity (i.e., the extent of brain cell death) [1].Stroke or brain attack is a sudden problem affecting the blood vessels of the brain. There are several types of stroke, and each type has different causes. The three main types of stroke are listed below. There is a third type referred to as transient ischemic attack (TIA) or "mini-stroke." While they are not true strokes because the symptoms are temporary, TIAs are usually a warning sign of a stroke to come. Heeding the warning signs of TIAs and treating the underlying risk factors that trigger them can prevent many strokes. The vast majority of strokes – approximately 83 percent — are ischemic. They are caused by an obstruction of an artery leading to or in the brain, preventing oxygenated blood from reaching parts of the brain that the artery feeds. Ischemic strokes are either thrombotic or embolic, depending on where the obstruction or clot (thrombus or embolism), causing the blockage originated:

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Thrombotic Ischemic Stroke

Thrombotic stroke is caused by a thrombus (blood clot) that develops in an artery supplying blood to the brain — usually because of a repeated buildup of fatty deposits, calcium and clotting factors, such as fibrinogen and cholesterol, carried in the blood. The body perceives the buildup as an injury to the vessel wall and responds the way it would to a small wound — it forms blood clots. The blood clots get caught on the plaque on the vessel walls, eventually stopping blood flow. There are two types of thrombotic stroke: Large vessel thrombosis, Small vessel disease. Thrombotic disease accounts for about 60 percent of acute ischemic strokes. Of those, approximately 70 percent are large vessel thrombosis [2].

Embolic Ischemic Stroke

A blood clot that forms in one area of the body and travels through the bloodstream to another where it may lodge is called an embolus. In the case of embolic stroke, the clot forms outside of the brain – usually in the heart or large arteries of the upper chest and neck – and is transported through the bloodstream to the brain. There it eventually reaches a blood vessel small enough to block its passage. Cardiac sources of embolism account for 80 percent of embolic ischemic strokes.

Hemorrhagic stroke occurs when a vessel in the brain suddenly ruptures and blood begins to leak directly into brain tissue and/or into the clear cerebrospinal fluid that surrounds the brain and fills its central cavities (ventricles). The rupture can be caused by the force of high blood pressure. It can also originate from a weak spot in a blood vessel wall (a cerebral aneurysm) or other blood vessel malformation in or around the brain. There are two types of hemorrhagic strokes. They are differentiated by where the ruptured artery is located and where the resulting blood leakage occurs. Intra cerebral Hemorrhage (ICH) (also called Intra parenchymal hemorrhage or intracranial hematoma).

This type of stroke is caused by the sudden rupture of an artery or blood vessel within the brain. The blood that leaks into the brain results in a sudden increase in pressure that can damage the surrounding brain cells. If the amount of blood increases rapidly, the sudden and extreme buildup in pressure can lead to unconsciousness or death. Approximately 10 percent of all strokes are intra cerebral hemorrhages. They occur most commonly in the basal ganglia where the vessels are particularly delicate.

Subarachnoid Hemorrhage (SAH)

Subarachnoid hemorrhage occurs when bleeding from a damaged vessel causes blood to accumulate between the brain and the skull, in the subarachnoid space, and press on the surface of the brain instead of dispersing into the tissue. The leaked blood can irritate damage or destroy surrounding brain cells.

When blood enters the subarachnoid space, it mixes with the cerebrospinal fluid (CSF) that cushions the brain and spinal cord. This can block CSF circulation, which leads to fluid buildup and increased pressure on the brain. The open spaces in the brain (ventricles) may enlarge, resulting in a condition called hydrocephalus. This can make a patient lethargic, confused or incontinent. The large accumulation of blood increases the pressure surrounding the brain, interfering with brain function.

The leaked blood also can produce a condition called vasospasm in which the vessels narrow, impeding the flow of blood to the brain. This can result in an ischemic stroke. The condition typically develops five to eight days after the initial hemorrhage.

Stroke Statistics

- Stroke remains the third leading cause of death, behind heart disease and cancer. Stroke is the leading cause of serious, long-term disability in the United States. In 1999, about 1,100,000 Americans reported difficulties with daily living because of a stroke.
- Each year, about 700,000 people suffer a stroke. About 500,000 of these are first attacks, and 200,000 are recurrent attacks.
- Stroke killed 275,000 people in 2002 and accounted for about 1 of 16 deaths in the United States.
- 28% of people who suffer a stroke in a given year are under age 65.
- Compared with white males 45 to 54 years old, African Americans males in the same age group have a threefold greater risk of ischemic stroke.
- About 50% of stroke deaths in 2003 occurred out of hospital.
- On average, someone in the United States suffers a stroke every 45 seconds; every 3 to 4 minutes, someone dies of a stroke.
- About 4.7 million stroke survivors (2.3 million men, 2.4 million women) are alive today.
- Among persons 45 to 64 years old, 8-12% of ischemic strokes and 37-38% of hemorrhagic strokes result in death within 30 days.
- Quitting smoking reduces your stroke risk to that of a non-smoker in five years.
- Sickle cell disease is the most important cause of ischemic stroke among African-American children.
- Within a year, up to 25% of people who had (TIA or "mini-stroke") will die.

SYMPTOMS OF STROKE

The symptoms of a stroke vary from person to

person. As different parts of our brain control different parts of our body, symptoms will depend upon the part of brain that has been affected, and the extent of the damage. The symptoms of a stroke usually come on suddenly, and can include:

1. Numbness, or weakness, down one side, ranging in severity from weakness in your hand, to complete paralysis of the whole side of your body,
2. Weakness in your face, which can make you drool saliva,
3. Dizziness,
4. Communication problems; difficulty talking and understanding what others are saying,
5. Problems with balance and coordination,
6. Difficulty swallowing,
7. Severe headaches, and
8. Loss of consciousness (in severe cases).

A good way of remembering the symptoms of a stroke is to remember the **word 'FAST'**, where:

1. 'F' stands for facial numbness, or weakness, particularly on one side,
2. 'A' stands for arm numbness, or weakness, particularly on one side,
3. 'S' stands for slurred speech, or difficulty understanding, and
4. 'T' stands for time, which is of the essence

It cannot be stressed enough how important prompt emergency treatment is for strokes. Typically, 1.9 million brain cells are lost for each minute a stroke goes untreated. Also, one of the treatments for strokes, known as thrombolysis (where medicines are used to remove blood clots), must begin not later than three hours after the stroke has occurred.

Effects of Stroke

Intellect, sensation, perception and movement, all honed over the course of a lifetime, are the very abilities most compromised by stroke. Stroke can rob people of the most basic methods of interacting with the world [3].

The specific abilities that will be lost or affected by stroke depend on the extent of the brain damage and, most importantly, on the location of the stroke in the brain. The brain is an incredibly complex organ, and each area within the brain has responsibility for a particular function or ability. The brain is divided into four primary parts: the right hemisphere (or half), the left hemisphere, the cerebellum and the brain stem.

Right-Hemisphere Stroke

The right hemisphere of the brain controls the movement of the left side of the body. It also controls analytical and perceptual tasks, such as judging distance, size, speed, or position, and seeing how parts are connected to wholes.

A stroke in the right hemisphere often causes paralysis in the left side of the body, known as left hemiplegia. Survivors of right-hemisphere strokes may also have problems with their spatial and perceptual abilities. This may cause them to misjudge distances (leading to a fall) or be unable to guide their hands to pick up an object, button a shirt or tie their shoes. They may even be unable to tell right-side up from upside down when trying to read. Along with their impaired ability to judge spatial relationships, survivors of right-hemisphere strokes often have judgment difficulties that show up in their behavioral styles. These patients often develop an impulsive style, unaware of their impairments and certain of their ability to perform the same tasks as before the stroke. This behavioral style can be extremely dangerous. It may lead the stroke survivor with left-side paralysis to try to walk without aid or it may lead the survivor with spatial and perceptual impairments to try driving a car. Survivors of right-hemisphere strokes may also experience left-sided neglect. Stemming from visual field impairments, left-sided neglect causes the survivor of a right-hemisphere stroke to “forget” or “ignore” objects or people on their left side [4].

Left-Hemisphere Stroke

The left hemisphere brain controls movement of the right side of the body .It also controls speech and language abilities for most people .A left hemisphere stroke often causes paralysis of the right side of the body. This is known as right hemiplegia. Someone who has had a left-hemisphere stroke may also develop aphasia. Aphasia is a term used to describe a wide range of speech and language problems. These problems can be specific, affecting only one part of the patient’s ability to communicate, such as the ability to move their speech-related muscles to talk properly. The same patient may be completely unimpaired when it comes to writing, reading or understanding speech. In contrast to survivors of right-hemisphere stroke, patients who have had a left-hemisphere stroke often develop a slow and cautious behavioral style. They may need frequent instruction and feedback to complete tasks. Finally, patients with left-hemisphere stroke may develop memory problems similar to those of right-hemisphere stroke survivors. These problems include shortened retention spans, difficulty in learning new information and problems in conceptualizing and generalizing.

Cerebellar Stroke

The cerebellum controls many of our reflexes and much of our balance and coordination. A stroke that takes place in the cerebellum can cause abnormal reflexes of the head and torso, coordination and balance problems, dizziness, nausea and vomiting [5].

Brain Stem Stroke

Strokes that occur in the brain stem are especially devastating. The brain stem is the area of the brain that controls all of our involuntary, "life-support" functions, such as breathing rate, blood pressure and heartbeat. The brain stem also controls abilities such as eye movements, hearing, speech and swallowing. Since impulses generated in the brain's hemispheres must travel through the brain stem on their way to the arms and legs, patients with a brain stem stroke may also develop paralysis in one or both sides of the body.

STROKE RISK FACTORS AND THEIR IMPACT

Stroke is one of the most preventable of all life-threatening health problems. Risk factors for stroke fall into two categories: those that can be controlled through lifestyle changes or medication and those that cannot.

Uncontrollable Stroke Risk Factors

Age

The chances of having a stroke increase with age. Two-thirds of all strokes happen to people over age 65. Stroke risk doubles with each decade past age 55.

Gender

Males have a slightly higher stroke risk than females. But, because women in the United States live longer than men, more stroke survivors over age 65 are women.

Race

African Americans have a higher stroke risk than some other racial groups. Hispanics also appear to have an increased risk of stroke, although not to the same degree as African Americans.

Family history of stroke or Transient Ischemic Attack (TIA)

Risk is higher for people with a family history of stroke or TIA.

Personal history of diabetes

People with diabetes have a higher stroke risk. This may be due to circulation problems that diabetes can cause. In addition, brain damage may be more severe and extensive if blood sugar is high when a stroke happens. Treating diabetes may help delay the onset of complications that increase stroke risk.

Controllable Stroke Risk Factors

***Treatable Medical Disorders that Increase Stroke Risk Include*:**

High Blood Pressure

Having high blood pressure, or hypertension, increases stroke risk four to six times. It is the single most important controllable stroke risk factor. High blood pressure is often called "the silent killer" because people can have it and not realize it, since it often has no symptoms. Hypertension puts stress on blood vessel walls and can lead to stroke from blood clots or hemorrhages [6].

Heart Disease

Coronary Heart Disease and High Cholesterol

High cholesterol can directly and indirectly increase stroke risk by clogging blood vessels and putting people at greater risk for coronary heart disease, another important stroke risk factor. High levels of cholesterol in the blood stream can lead to the buildup of plaque on artery walls, which can clog arteries and cause a heart or brain attack.

Atrial fibrillation

Heart diseases such as atrial fibrillation increases stroke risk up to six times. AF raises stroke risk because it allows blood to pool in the heart. When blood pools, it tends to form clots which can then be carried to the brain, causing a stroke.

Personal history of stroke or TIA

People who have already had a stroke or TIA are at risk for having another. After suffering a stroke, men have a 42 percent chance of recurrent stroke within five years, and women have a 24 percent chance of having another stroke. TIAs are also strong predictors of stroke because 35 percent of those who experience TIAs have a stroke within five years.

Lifestyle Factors that Increase Stroke Risk Include

Smoking

Smoking doubles stroke risk. Smoking damages blood vessel walls, speeds up the clogging of arteries by plaque deposits, raises blood pressure and makes the heart work harder [7].

Alcohol

Drinking more than two drinks per day may increase your risk for stroke by almost half. Recent studies have also suggested that light to moderate alcohol consumption (up to two 4 oz. glasses of wine or the alcohol equivalent) may protect against stroke by raising levels of a naturally occurring "clot-buster" in the blood.

Weight

Excess weight puts a strain on the entire circulatory system. It also makes people more likely to have other stroke risk factors such as high cholesterol, high blood pressure and diabetes.

DIAGNOSIS

Brain imaging

Strokes are usually diagnosed by studying images of the brain (brain imaging). This can also be helpful in determining the risk of a transient ischemic attack (TIA). Even if the physical symptoms of a stroke are obvious, brain imaging should be carried out in order to determine

whether an ischemic stroke, or a hemorrhagic stroke, has occurred. This is important because different treatment is required for each condition, and treating a hemorrhagic stroke with the methods used for an ischemic stroke, will make the condition worse.

CT and MRI scans

Two common methods that are used for brain imaging are a computer topography (CT) scan and a magnetic resonance (MRI) scan.

Other tests

A number of other tests will also be carried out to try and identify the cause of the stroke. These include:

1. a blood pressure test,
2. blood tests to measure factors such as your cholesterol level or, if you are diabetic, your glucose level, and
3. an echocardiogram, which is an image of your heart that is produced using sound waves.

TREATMENT

Early treatment can help minimize damage to brain tissue and improve the outcome (prognosis). Treatment depends on whether the stroke is ischemic or hemorrhagic and on the underlying cause of the condition. The long-term goals of treatment include rehabilitation and prevention of additional strokes [8].

Ischemic Stroke

Initial treatment for ischemic stroke involves removing the blockage and restoring blood flow.

Tissue plasminogen activator (t-PA) is a medication that can break up blood clots and restore blood flow when administered within 3 hours of the event. This medication carries a risk for increased intracranial hemorrhage and is not used for hemorrhagic stroke. Mannitol, a diuretic, may be administered intravenously (through an I.V) to reduce intracranial pressure during an ischemic stroke.

Antihypertensives such as labetalol and enalapril may be used alone or in combination with diuretics to treat high blood pressure.

Antiplatelet agents such as aspirin, clopidogrel bisulfate, and aspirin with dipyridamole may be prescribed to reduce the risk for recurrent stroke. Aspirin may also improve the outcome of a stroke when administered within 48 hours.

Clopidogrel bisulfate is an antiplatelet medication that is taken orally, once a day, to help prevent the formation of blood clots. It is prescribed for patients with atherosclerosis who have had a recent stroke and is used to prevent recurrence.

Anticonvulsants such as diazepam and lorazepam may be prescribed for patients who experience recurrent seizures after a stroke.

Anticoagulants such as warfarin may be prescribed to prevent the formation of blood clots. Patients taking warfarin may require regular blood tests to monitor coagulation (blood clot formation) and prevent abnormal bleeding [9].

Hemorrhagic Stroke

Hemorrhagic stroke usually requires surgery to relieve intracranial (within the skull) pressure caused by bleeding. Most of the damage caused by this type of stroke results from the physical disruption of brain tissue. Surgical treatment for hemorrhagic stroke caused by an aneurysm or defective blood vessel can prevent additional strokes. Surgery may be performed to seal off the defective blood vessel and redirect blood flow to other vessels that supply blood to the same region of the brain.

Endovascular treatment involves inserting a long, thin, flexible tube (catheter) into a major artery, usually in the thigh, guiding it to the aneurysm or the defective blood vessel, and inserting tiny platinum coils (called stents) into the blood vessel through the catheter. Stents support the blood vessel to prevent further damage and additional strokes [10].

Rehabilitation

Recovery and rehabilitation are import aspects of stroke treatment. In some cases, undamaged areas of the brain may be able to perform functions that were lost when the stroke occurred. Rehabilitation includes physical therapy, speech therapy, and occupational therapy.

Physical therapy involves using exercise and other physical means (e.g., massage, heat) to help patients regain the use of their arms and legs and prevent muscle stiffness in patients with permanent paralysis.

Speech therapy helps patients regain the ability to speak.

Occupational therapy helps patients regain independent function and relearn basic skills.

Prognosis

Prognosis depends on the type of stroke, the degree and duration of obstruction or hemorrhage, and the extent of brain tissue death. Most stroke patients experience some permanent disability that may interfere with walking, speech, vision, understanding, reasoning, or memory.

Approximately 70% of ischemic stroke patients are able to regain their independence and 10% recover almost completely. Approximately 25% of patients die as a result of the stroke. The location of a hemorrhagic stroke is an important factor in the outcome, and this type generally has a worse prognosis than ischemic stroke [11].

STROKE PREVENTION GUIDELINES

In 1998, National Stroke Association's (NSA) Prevention Advisory Board released its Stroke Prevention Guidelines. These guidelines were the first-ever national expert consensus set of recommendations on what the public can do to prevent stroke. In 1999, NSA released more detailed medical guidelines for professionals.

The Prevention Advisory Board is comprised of the nation's leading experts on stroke prevention.

Stroke Is Preventable

National Stroke Association Stroke Prevention Guidelines

1. Know your blood pressure. Have it checked at least annually. If it is elevated, work with your doctor to control it.
2. Find out if you have atrial fibrillation (also called AF). If you have AF work with your doctor to manage it.
3. If you smoke, stop.
4. If you drink alcohol, do so only in moderation.
5. Know your cholesterol number. If it is high, work with your doctor to control it.
6. If you are diabetic, follow your doctor's recommendations carefully to control your diabetes.
7. Include exercise in the activities you enjoy in your daily routine.
8. Enjoy a lower sodium (salt), lower fat diet.
9. Ask your doctor if you have circulation problems which increase your risk for stroke. If so, work with your doctor to control them.
10. If you have any stroke symptoms, seek immediate medical attention.

Explanation

Brain injury following permanent and transient brain ischemia develops from a complex series of pathophysiological events that evolve with time and affect specific brain regions. The impairment of CBF to below 20 to 30% of normal levels initiates these pathophysiological events (Fig 2). In the acute period (varying from a few minutes to hours), the impairment of CBF restricts the delivery of energy, O_2 and glucose, and thus impairs the production of ATP required to maintain cellular ionic pumps, such as the Na^+-K^+ channel. Disability of the Na^+-K^+ channel results in depolarization of the plasma membrane, rapid loss of K^+ from neurons, massive influx of water with the influx of Na^+ and Cl^- and induction of cytotoxic edema.

In addition, the brain ischemia causes a disruption of the blood brain barrier (BBB). Disruption of the BBB increases percolation of fluid from vessels into the brain parenchyma and results in vasogenic edema. The ensuing edema can negatively affect perfusion deficits, and also have distant effects on perfusion produced via increased intracranial pressure, vascular compression, and herniation. This period also evokes glutamate release, an extracellular excitatory amino acid, hich activates excitatory amino acid receptors such as N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), and opens voltage-sensitive Ca2+ channels. Therefore, intracellular Ca2+([Ca2+]) increases are clearly implicated in the neurotoxic process [12].

After a few hours to a few days, over-stimulation of the NMDA-receptor, following Ca_2^+ influx, glial cell activation causes the expression of cytotoxic pro-inflammatory cytokines, such as tumor necrosis factor α (TNFα), interleukin-1β (IL-1β), and nitric oxide synthase (NOS) that play a central role in this sub-acute phase. The cytokines and NOS, directly or indirectly, lead to the generation of reactive oxygen species (ROS) and the formation of excessive amounts of free radicals, including NO, superoxide anion ($O2^-$), hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO^-$). Elevated Ca_2^+ in the mitochondria uncouples oxidative phosphorylation, leading to a further decrease in energy supply and an increase in free radicals. These free radicals damage cellular membranes by lipid peroxidation. A second cytotoxic pathway also comes into play by the sustained activation of a large range of Ca_2^+ dependent enzymes, such as lipases, proteases, endonucleases and other catabolic enzymes. These degradative enzymes collectively have detrimental consequences on cell function, membrane structure, and the cytoskeleton, and ultimately lead to neuronal cell death. Even if blood flow is restored, the addition of oxygen can actually enhance the biochemical reactions present that generate ROS. Another component that contributes to cell damage is inflammation. In the ischemic zone, endothelial adhesion receptors are up regulated and leukocytes migrate through the walls of blood vessels, invade the parenchyma and release their cytotoxic cytokines, NOS and ROS. In conclusion, ischemic brain damage is multidimensional in origin and offers a broad range of targets for neuroprotective intervention.

After a few days, cell death, including delayed neuronal cell death (DNCD), leads to ischemic penumbra which is, in part, also the product of apoptotic processes, including the caspase cascade induced by TNFα and the oxidation of mitochondria. DNA damage via endonucleases or free radicals triggers a complex self-destructive process involving a regulated pattern of gene expression. As a consequence, neurons die apoptotically, and there is growing evidence that mitochondria are the key structures for the induction of this programmed cell death [13].

Ischemic Core and Penumbra

Ischemia develops within minutes, forming two zones around the site of thrombosis or embolism. Brain cells at the center of ischemic region where the cerebral

circulation is completely arrested, irreversible cell damage occurs in several minutes. However, cells in the area surrounding the center, the ischemia is incomplete because of the presence of perfusion from collateral vessels. This region is called penumbra, where reduced blood flow falls to the level below the threshold for electrical failure and above the threshold for energy failure. Restoration of cerebral blood flow, even to a sub-optimal level, provides an opportunity for those brain cells to recover and regain functionality [14].

Energy Failure

When blood flow is interrupted, the supply of glucose and oxygen (the substrates of aerobic metabolism) ceases. Stores of glucose and glycogen are scant in the brain, but residual glucose is metabolized anaerobically in both astrocytes and neurons, resulting in lactate accumulation and acidosis. Since lactate cannot be metabolized further due to lack of oxygen, energy failure and an altered redox state with accumulation of NADH ensue. The acidosis can be detrimental in itself, as it alters cell metabolism and mitochondrial membrane function. Pyruvate dehydrogenase is inhibited in mitochondria that have been ischemic, which contributes to prolonged acidosis, even if ischemia is transient.

Role of Calcium

Calcium accumulates intracellularly because of membrane depolarization and ionotropic NMDA-receptor activation. The increase in the intracellular calcium level can be dramatic (from O.1 to 3O mM in hippocampal CA1 neurons), and has a central role in both acute cell dysfunction or destruction and secondary brain damage,

The sharp increase of intracellular calcium concentration is the principal death-signalling event in both necrosis and apoptosis, resulting in the subsequent activation of calpains. Activated calpains cleave NMDA and NCX channels. NMDA remains active, whereas NCX, which is involved in calcium extrusion, becomes inactivated. Both these events contribute to further elevation of intracellular calcium. Depending on the level of calpain activation, neurons might undergo apoptotic or necrotic death. The left side of the figure illustrates events underlying neuronal death showing predominantly apoptotic features. The direct link between calpains and cathepsins (right side) is supported by findings in nematode and primate neurons undergoing necrotic cell death. However, lysosomal damage and activation of cathepsins might occur independently of calpains. Dashed arrows point to identified protease targets [15].

Glutamate and Excitotoxiciy

Despite its ubiquitous role as a neurotransmitter, glutamate is highly toxic to neurons, a phenomenon dubbed *excitotoxicity* a low concentration of glutamate applied to neurons in culture kills the cells, and the finding in the 1970s that glutamate given orally produces neurodegeneration in vivo caused considerable alarm because of the widespread use of glutamate as a 'taste-enhancing' food additive [16].

Calcium overload is the essential factor in excitotoxicity. The mechanisms by which this occurs and leads to cell death are as follows:

1. Glutamate activates NMDA, AMPA and metabotropic receptors (sites 1, 2 and 3). Activation of AMPA receptors depolarises the cell, which unblocks the NMDA channels, permitting Ca^{2+} entry. Depolarisation also opens voltage-activated calcium channels (site 4), releasing more glutamate. Metabotropic receptors cause the release of intracellular Ca^{2+} from the endoplasmic reticulum. Na^{+} entry further contributes to Ca^{2+} entry by stimulating Ca^{2+}/Na^{+} exchange (site 5). Depolarisation inhibits or reverses glutamate uptake (site 6), thus increasing the extracellular glutamate concentration.
2. The mechanisms that normally operate to counteract the rise in $[Ca^{2+}]_i$ include the Ca^{2+} efflux pump (site 7) and, indirectly, the Na^{+} pump (site 8).
3. The mitochondria and endoplasmic reticulum act as capacious sinks for Ca^{2+} and normally keep $[Ca^{2+}]_i$ under control. Loading of the mitochondrial stores beyond a certain point, however, disrupts mitochondrial function, reducing ATP synthesis, thus reducing the energy available for the membrane pumps and for Ca^{2+} accumulation by the endoplasmic reticulum. Formation of reactive oxygen species is also enhanced. This represents the danger point at which positive feedback exaggerates the process.
4. Raised $[Ca^{2+}]$ affects many processes, the chief ones relevant to neurotoxicity being: increased glutamate release activation of proteases (calpains) and lipases, causing membrane damage activation of nitric oxide synthase; while low concentrations of nitric oxide are neuroprotective, high concentrations in the presence of reactive oxygen species generate peroxynitrite and hydroxyl free radicals, which damage many important biomolecules, including membrane lipids, proteins and DNA increased arachidonic acid release, which increases free radical production and also inhibits glutamate uptake [17].

Radical Oxygen Species (ROS)

Oxygen (free) radicals are extremely reactive molecules implicated in ischemic brain damage, expecially reperfusion injury. In normal physiology, they are continuously formed in small amounts as biproducts of oxidative metabolism. Free radicals are also used by macrophages, T-killer cells and other leukocytes in inflammation and combatting infection

In the classical view of cerebral ischemia, reperfusion of ischemic tissue leads to grossly enhanced

ROS production (triggered by intracellular calcium via conversion of xanthine dehydrogenase to xanthine oxidase and activation of phospholipases). This causes activation of arachidonic acid cascades and lipid peroxidation, protein oxidation and DNA damage, leading to cell membrane damage, swelling and necrosis.

Mitochondrial Dysfunction

Brain mitochondria are sensitive to ischemic injury, and exhibit signs of impaired function after periods of moderately reduced blood flow, even when ATP and phosphocreatine levels are not significantly affected. In fact, "incomplete" ischemia may result in greater mitochondrial damage than "complete" ischemia, due to the immediate action of ROS. The consequences of mitochondrial injury after cerebral ischemia thus depend on the severity of ischemia and reperfusion, and include cellular energy failure (abolished ATP production), oxidative stress (ROS), exacerbation of excitotoxicity through impaired calcium buffering (mitochondria are normally an important part of regulating intracellular calcium homeostasis). Furthermore, calcium overload in mitochondria can cause mitochondrial swelling or opening of a non-specific proteinacious pore (the mechanisms have not been completely clarified) and membrane permeability increase, or if less severe, expulsion of cytochrome C, which interacts with caspases and results in apoptosis. With complete ischemia, different patterns of pathophysiological events have been shown to occur depending on the duration of ischemia. With short duration (up to 2O minutes), energy failure is reversible, but reperfusion triggers a cascade of events that lead to delayed cell death. In this setting, there is a differentiation of brain cells as to the sensitivity to ischemia, reflected in the tendency to develop apoptosis. With up to a few hours of complete ischemia, partial irreversible injury to the electron transport chain is seen, exacerbated by reperfusion. With longer duration of severe ischemia, mitochondrial function is completely disrupted, and cells rapidly develop necrosis [18].

Inflammatory Cascade

Several pro-inflammatory cascades are initiated within minutes after the onset of stroke. These events are promoted, in part, by the binding of cell adhesion molecules (e.g., selectin and intercellular adhesion molecule (ICAM) expressed in endothelial cells with integrins expressed on the neutrophil surface. The inflammatory mediators are generated by reactive microglia, neurons, astrocytes, or macrophages and leukocytes recruited into the ischemic brain. There is transient upregulation of immediate early genes encoding transcription factors (e.g., fos and jun) within minutes of occlusion. This is followed by a wave of expression of heat shock genes (e.g., Hsp70, Hsp72) within 1-2 hours. A third wave follows hours to days after the onset of stroke, at these time intervals several chemokines and cytokines are expressed [e.g., IL1, IL6, IL8, TNF-α, monocyte chemo attractant protein-1 (MCP1), etc]

Oxidative Stress

Oxidative stress has been defined as "an imbalance between oxidants and antioxidants in favor of the oxidants, potentially leading to damage". Oxidative stress has been involved in aging as well as in the pathogenesis of several diseases (atherosclerosis, cancer, neurodegenerative diseases including Alzheimer's dementia, stroke). When free radicals overcome the cellular antioxidant defense, oxidative stress takes place potentially leading to damage of all the principal cellular molecules. The brain is especially prone to free radical damage for several reasons. First it is very rich in polyunsaturated fatty acids, which are particularly vulnerable to free radical induced peroxidation. Then it has a low content of antioxidant enzymes, such as catalase and glutathione peroxidase, while it contains a significant amount of iron despite its iron binding capacity is not very high. Iron ions are known to stimulate free radical generation .Both neuronal necrosis and apoptosis can be induced by oxidative stress [19].

Apoptotic Cell Death Pathways

Many of the key molecular events in programmed cell death have now been determined. Just as calcium entry into the neuron is a key step in excitotoxicity, the release of cytochrome *c* from the mitochondria is a key event in initiating apoptosis in many cell types. Cytosolic cyto-chrome *c* complexes with APAF-1 and procaspase 9. As a result, procaspase 9 is cleaved into its active form, caspase 9. Caspase 9 then cleaves and activates other caspases, including caspase 3. The molecular mechanisms by which programmed cell death is initiated are numerous and complex. Programmed cell death may be activated via cell surface receptors, including the Fas receptor and tumor necrosis factor-α (TNF- α). Activation of these receptors triggers activation of caspase 8, which in turn cleaves the bcl-2 family protein bid.The cleaved bid then translocates from the cytoplasm to the mitochondria, where it initiates cytochrome *c* egress. Other mechanisms by which the initiation of programmed cell death is controlled include the ERK (externally regulated kinase) and JNK protein kinase cascades. Finally, DNA base oxidation and other DNA damage may initiate programmed cell death via expression of the p53 transcription factor. The result is cleavage of DNA between histosomes, a hallmark of programmed cell death [20].

Reactive oxygen species (ROS) contribute to stroke injury

ROS including hydrogen peroxide (H_2O_2) and superoxide radical (O_2^{-}) are produced by a number of

cellular oxidative metabolic processes involving xanthine oxidase, NAD(P)H oxidases, metabolism of arachidonic acid by cyclooxygenases and lipoxygenases, monoamine oxidases, and the mitochondrial respiratory chain. The involvement of phospholipase A_2 (PLA_2) in ROS formation is outlined. ROS can also be formed nonenzymatically, for example, by autoxidation of catecholamines.

Endogenous defenses that detoxify ROS include enzymatic systems such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GSH-Px), and nonenzymatic antioxidants such as ascorbic acid, vitamin E, β-carotene, and glutathione (GSH). Neurons may be particularly vulnerable to free radical damage since they contain low levels of GSH .While ROS are proposed to play important roles in coordinating and regulating a number of cellular signaling pathways (redox signaling), oxidative stress results when the formation of ROS exceeds the capacity of antioxidant defense systems [21].

ROS and reactive nitrogen species (RNS) initiate lipid peroxidation

The highly reactive hydroxyl radical (SOH) is not produced as a by-product of any known enzymatic reaction, but is formed from H_2O_2 (in itself not highly reactive) in the presence of divalent metal ions, especially Fe^{2+} and Cu^{2+}, via the Fenton reaction. Once formed, ·OH reacts almost instantaneously with many cellular components, including polyunsaturated fatty acids of membrane lipids. The initial reaction of ·OH with polyunsaturated fatty acids produces an alkyl radical, which in turn reacts with molecular oxygen to form a peroxyl radical (ROOS). The ROOS can abstract hydrogen from an adjacent fatty acid to produce a lipid hydroperoxide (ROOH) and a second alkyl radical, propagating a chain reaction of lipid oxidation.

Nitric oxide (·NO) is formed by enzymatic oxidation of L-arginine to citrulline by nitric oxide synthases and serves as an important regulator of vascular response and neuronal signaling. O_2 ·¯does not directly induce lipid peroxidation, but can react with ·NO to form peroxynitrite ($ONOO^-$), a strong oxidant that can initiate lipid peroxidation Lipid peroxidation is not the sole route of cellular damage initiated by ·OH and $ONOO^-$ as these species also oxidize proteins and DNA [22].

Lipid peroxidation products can alter cellular function

Peroxidation of lipids can disrupt the organization of the membrane, causing changes in fluidity and permeability, inhibition of metabolic processes, and alterations of ion transport. Damage to mitochondria induced by lipid peroxidation can lead to further ROS generation. In addition, lipid peroxides degrade to reactive aldehyde products, including malondialdehyde (MDA), 4-hydroxynonenal (HNE), and acrolein . These aldehydes in turn covalently bind to proteins through reaction with thiol groups and alter protein function (Fig:14). They can also react with amino groups of guanosine to form cyclic adducts. Among all α,β-unsaturated aldehydes, acrolein is by far the strongest electrophile and shows the highest reactivity with proteins . Overproduction of lipid peroxides and aldehyde products can cause depletion of GSH through detoxification by GSH-Px and glutathione S-transferase [23].

*Chan P.H et al*Oxygen free radicals or oxidants have been proposed to be involved in acute central nervous system injury that is produced by cerebral ischemia and reperfusion. Because of the transient nature of oxygen radicals and the technical difficulties inherent in accurately measuring their levels in the brain, experimental strategies have been focused on the use of pharmacological agents and antioxidants to seek a correlation between the exogenously supplied specific radical scavengers (ie, superoxide dismutase and catalase) and the subsequent protection of cerebral tissues from ischemic injury. However, this strategy entails problems (hemodynamic, pharmacokinetic, toxicity, blood-brain barrier permeability, etc) that may cloud the data interpretation [24-36].

Antioxidant Enzyme SODs and Cerebral Ischemia

Several enzymes, including SOD, GSHPx, glutathione reductase, and catalase, are endogenous antioxidants that process specific free radical scavenging properties. SODs, in particular, have been used extensively to reduce superoxide radical-associated ischemic brain damage.

Based on the metal ion requirements and the anatomic distribution, three types of SODs exist in brain cells. CuZn-SOD is a cytosolic enzyme that requires both copper and zinc ions as cofactors. It is a dimeric protein that is coded by the human CuZn-SOD transgene (SOD-1) on chromosome 21 in human cells. Manganese (Mn-SOD) is a mitochondrial enzyme with requirements for Mn^2 plus. It is a tetrameric protein that is coded by the SOD-2 gene in chromosome 4 in human cells. Both CuZn-SOD and Mn-SOD from various sources have been fully characterized biochemically, and the cDNAs of both human enzymes have been successfully cloned. A copper-containing SOD (sod-3) has been identified in the extracellular space, and its gene has been successfully cloned as specified for superoxide radicals, CuZn-SOD has been used extensively to reduce brain injury induced by ischemia and reperfusion. Unfortunately, investigators have obtained various degrees of success and failure when free nonmodified SOD was used to ameliorate ischemic brain injury. The extremely short half-life of CuZn-SOD (6 minutes) in circulating blood and its failure to pass the

blood-brain barrier make it difficult to use enzyme therapy in cerebral ischemia. However, a modified enzyme with an increased half-life, such as polyethylene glycol-conjugated SOD, has been successfully used to reduce infarct volume in rats that have been subjected to focal cerebral ischemia. Liposome-entrapped SOD has an increased half-life (4.2 hours), blood-brain barrier permeability, and cellular uptake, and it has also proved to be an effective treatment in reducing the severity of traumatic and focal ischemic brain injuries. Yet, in some instances, modified SOD (ie, polyethylene glycolconjugated SOD) has been used with conflicting results. The fact that the results are mixed make it imperative to use other experimental strategies so the role of SOD can be fully established in cerebral ischemia [37-41].

REFERENCES

1. Valery L, Feigin Faan. Herbal Medicine in Stroke Does It Have a Future. *Stroke*, 38, 2007, 1734-1736.
2. World Health Organization. *World Health Organization Fact Sheet.* Revised May 2003 ed. Geneva: World Health Organization; 2003.
3. Teng L, Shaw D, Barnes J. Traditional Chinese herbal medicine. *The Pharmaceutical Journal*, 276, 2006, 361–363.
4. Kim H. Neuroprotective herbs for stroke therapy in traditional eastern medicine. *Neurol Res*, 27, 2005, 287–301.
5. Gong X, Sucher NJ. Stroke therapy in traditional Chinese medicine (TCM): prospects for drug discovery and development. *Phytomedicine*, 9, 2002, 478-484.
6. Shiflett SC. Overview of complementary therapies in physical medicine and rehabilitation. *Physical Medicine & Rehabilitation Clinics of NorthAmerica*, 10, 1999, 521-529.
7. Zeng X, Liu M, Yang Y, Li Y, AsplundK. Ginkgo biloba for acute ischemic stroke. *Cochrane Database of Systematic Reviews*, 2005.
8. Wu B, Liu M, Zhang S. Dan Shen agents for acute ischemic stroke. *Cochrane Database of Systematic Reviews*, 4, 2004, 4295.
9. Wang NL, Liou YL, Lin MT, Lin CL, Chang CK. Chinese herbal medicine, Shengmai San, is effective for improving circulatory shock and oxidative damage in the brain during heat stroke. *Journal of Pharmacological Sciences*, 97(2), 2005, 253-65.
10. Lee IY, Lee CC, Chang CK, Chien CH, Lin MT, Sheng Mai San. Chinese herbal medicine protects against renal ischemic injury during heat stroke in the rat. *Clinical & Experimental Pharmacology & Physiology*, 32, 2005, 742-748.
11. Bei W, Peng W, Ma Y, Xu A. Nao Xin Qing. An anti-stroke herbal medicine, reduces Hydrogen peroxide-induced injury in NG108–15 cells. *Neuroscience Letter*, 363, 2004, 262-265.
12. Feigin VL. Stroke in developing countries: can the epidemic be stopped and outcomes improved. *The Lancet Neurology*, 6, 2007, 94-97.
13. Gagnier JJ, Boon H, Rochon P, Moher D, Barnes J, Bombardier C. Reporting randomized, controlled trials of herbal interventions: an elaborated consort statement. *Ann Intern Med*, 144, 2006, 364-371.
14. Gagnier JJ, Boon H, Rochon P, Moher D, Barnes J, Bombardier C. Recommendations for reporting randomized controlled trials of herbal interventions: explanation and elaboration.*J ClinEpidemiol*, 59, 2006, 1134-1149.
15. NishrithaBopana, Sanjay Saxena.Asparagus racemosus-Ethnopharmacological evaluation and conservation needs. *Journal of Ethanopharmacology*, 110(1), 2007, 1-15.
16. National Stroke Association's Complete Guide to Stroke. 1st edition :2003
17. Types of stroke: 2002. URL: http://*www.stroke center.org*_types/htm.
18. Explanation about types of stroke. URL: http://*www.Theuniversityhospital.com/stroke/htm.*
19. Symptoms of stroke. URL: *http://www.stroke.org/site/Docserver/NSA_complete_guide.pdf*
20. U.S. Centers for Disease Control and Prevention and the Heart Disease and Stroke Statistics - 2007 Update, published by the American Heart Association.
21. Smith D. Stroke Prevention: The Importance of Risk Factors, *Stroke: Clinical Updates, National Stroke Association*, 5, 1991, 17-20.
22. NHLBI, National Institutes of Health. *Morbidity & Mortality: 1998Chart book on Cardiovascular, Lung and Blood Diseases*, October 1998.
23. National Institutes of Health. National Institute of Neurological Disorders and Stroke. *Stroke: Hope through Research*. www.ninds.nih.gov, May 1999.
24. Barnett, Henry JM. *Stroke: Pathophysiology, Diagnosis and Management.* New York. Churchill Livingstone, 2nd ed. 1992, 3-27.
25. Connolly S. Stroke reduction in elderly patients (>75 years) with atrial fibrillation. *Lancet*, 343, 1994, 1509.
26. Grotta JC. Aspirin in stroke prevention. *Stroke Clinical Updates*, 1990; 1, 1990, 1-4.
27. Hass SW, Ticlodipine, An antiplatelet drug useful in stroke prevention. *Stroke:Clinical Updates*, 2, 1992, 21.

28. HirokazuOhtaki, Kenji Dohi, TomoyaNakamachi, Sachiko Yofu, Sakura Endo, Yoshifumi Kudo and Seiji Shioda. Evaluation of Brain Ischemia in Mice. *ActaHistochem. Cytochem*, 38(2), 2005, 99-106.
29. Gupta YK, Seema Briyal. Animal models of cerebral ischemia for evaluation of drugs. *Indian J Physiol Pharmacol*, 48 (4), 2004, 379-394.
30. Peter Frykholm. Cerebral ischemia studied with positron emission tomography and microdialysis, Uppsala, *Actauniversitatis*, 2002.
31. Annette T. Estrogen-inducible neuropeptide in the rat brain: role in focal ischemic lesions, *Linkoping*, 2005, 1- 93.
32. Marta Artal-Sanz, NektariosTavernarakis.Proteolytic mechanisms in necrotic cell death and neurodegeneration. *FEBS Letters*, 579, 2005, 3287-329.
33. Rang and Dale's *Pharmacology* 6th edition, 509-512.
34. Chan Ph. Reactive oxygen radicals in signaling and damage in the ischemic brain. *J. CerebBlood Flow Metabolism*, 21, 2001, 2-14.
35. Jinatta Jittiwat, Jintanaporn Wattanathorn, Terdthai Tong-un, Supaporn Muchimapura, Chuleeratana Bunchonglikitkul. The Neuroprotective effect of CF1 extract against Stroke, Khonkaen university, Thailand.
36. Murphy AN, Fiskum G, Beal MF. Mitochondria in Neurodegeneration: Bioenergetic Function in Cell Life and Death. *J Cereb Blood Flow Metab*, 19, 1999, 231-45.
37. Fiskum G, Murphy AM, Beal MF. Mitochondria in Neurodegeneration: Acute Ischemia and Chronic Neurodegenerative Diseases. *J Cereb Blood Flow Metab*, 19, 1999, 351-69.
38. Frijns CJ, Kappelle LJ. Inflammatory cell adhesion molecules in ischemic cerebrovascular disease. *Stroke*, 33, 2002, 2115-2122.
39. Madrigal JL, Moro MA, Lizasoain I, Lorenzo P, Leza JC. Stress-induced increase in extra cellular sucrose space in rats is mediated by nitric oxide. *Brain Res*, 938, 2002, 87-91.
40. Halliwell B, Reactive oxygen species and the central nervous system. *J. Neurochem*, 59, 1992, 1609-1623.
41. Yuh-Chiang Shen, Young-JiShiao, Yen-Jen Sung and Chuen-Neu Wang. Pathogenesis of Neurodegenerative diseases and the effect of natural products on nitric oxide production implicating in these diseases. *J Chin Med*, 16(2-3), 2005, 63-87.