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Pathophysiology of parenchymal injury in ischemic stroke

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ABSTRACT

Stroke is rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with no apparent cause other than of vascular origin. By definition, symptoms should last a minimum of 24 hours or result in death. Clinic may occur in two ways: "ischemic" as a result of vessel (arterial or venous) occlusion and "hemorrhagic" (intraparenchimal or subaracnoid) as a result of distruption of vascular integrity. Treating a disease requires an understanding of its mechanism. Over the years much progress has been made in elucidating the patophysiology of ischemic stroke. Current treatment trials have concentrated on distrupting these mechanisms from various points, restoring circulation and preserving the surviving neurons (neuroprotection)).5,6 In this review, hemorrhagic events were excluded due to the breadth of the subject. Current information on the pathophysiology of ischemic stroke and suggestions for the use of said information in treatment were brought together.

Keywords: Stroke, ischemic stroke, parenchymal injury

INTRODUCTION

According to the World Health Organization (WHO)'s description; stroke is rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with no apparent cause other than of vascular origin. By definition, symptoms should last a minimum of 24 hours or result in death.[1-3] Clinic may occur in two ways: "ischemic" as a result of vessel (arterial or venous) occlusion and "hemorrhagic" (intraparenchimal or subaracnoid) as a result of distruption of vascular integrity.[2] Ischemic strokes account for 62.4% of all global stroke incidents (7.63 million [95% CI, 6.57–8.96 million]), while ICHs for 27.9% (3.41 million, [95% CI, 2.97–3.91 million]), and SAHs for 9.7% (1.18 million [95% CI, 1.01–1.39 million]).[3,4] These percentages may vary in accordance with race, etnicity and country's development level.

According to data from GBD (Global Burden of Disease) study and AHA (American Hearth Association); stroke, with an incidence of 11.71 million and a prevalence of 89.13 million worldwide, is the leading cause of morbidity and ranks fifth among all causes of mortality in USA.[4] Approximately 30% of stroke patients die within the first year and one-third of those who survive remain disabled in basic acitivites of daily life.[2] According to same sources, ≈795 000 people have a new or recurrent stroke each year in USA. 610 000 of these are new and 185 000 are recurrent.[4] Unfortunately, treatment options are still limited to revascularization techniques, which can only be applied to a limited group of patients in the acute period. Moreover, with these techniques, only damaged tissue formation is prevented and the damage that has already been done cannot be reversed. In addition, secondary cell death following primary damage increases long-term disability since it cannot be prevented with current treatment methods.[5,6] Therefore, new approaches in treatment is necessary.

Treating a disease requires an understanding of its mechanism. Over the years much progress has been made in elucidating the patophysiology of ischemic stroke. Current treatment trials have concentrated on distrupting these mechanisms from various points, restoring circulation and preserving the surviving neurons (neuroprotection).[5,6] In this review, hemorrhagic events were excluded due to the breadth of the subject. Current information on the pathophysiology of ischemic stroke and suggestions for the use of said information in treatment were brought together.

MECHANISMS OF BRAIN PARENCHYMA DAMAGE

1. Ischemia and Hypoxia

Brain is an organ with high metabolic activity. Although it constitues only 2% of the total body weight, the normal brain receives 15% of the cardiac output and garners 20% of body's oxygen consumption (750 ml/min). Neurons mostly

rely on glucose as their energy source. However their ability to store it in glycogen form is negligible. As a result, all these factors make the brain tissue highly susceptible to changes in blood flow and therefore amount of oxygen and glucose transported through the blood.[2,7,8] Ischemia occurs when the delivery of oxygenated blood is less than the level needed to meet methabolic demands of the brain tissue.[7,10]

The ischemic tissue is composed of two parts. The "ischemic core" in the center; which suffers maximum damage from ischemia, whose recovery is not possible under current conditions; and the area surrounding the ischemic core, "penumbra", where energy metabolism is disrupted, electrical activity cannot be maintained, but irreversible cell death has not yet begun because it can maintain the ion balance between intracellular and extracellular space. Penumbra region, which is known to be salvageable, forms the basis of early treatment studies in acute ischemic stroke. In individuals with good collateral leptomeningeal flow, the core area remains smaller and the salvageable penumbra tissue remains larger. Today, it has been proven that if the presence of penumbra is demonstrated with the current imaging techniques, it is possible for acute ischemic stroke patients to benefit from thrombectomy treatment even after the 6 hour limit.[2,3]

On a cellular level, all parenchymal injury mechanisms seen during ischemic stroke can be divided into two groups: primary and secondary. Primary injury is irreversible damage that occurs within a few minutes of the incident which forms the ischemic core. In the primary injury zone, cells undergo necrosis. Necrosis is a passive event characterized by initial cellular and organelle swelling- which causes uncontrolled water intake into cell or in other words "cytotoxic edema"-, subsequent disruption of organelle and plasma membranes, disintegration of nuclear structure and cytoplasmic organelles with extrusion of cell contents into the extracellular space. Scattered cell content paves the way for secondary injury.[7,10]

Secondary injury is the name given to all the changes that primary injury triggers or happens after primary injury. These include not only unrecovered penumbra tissue but also areas damaged by the compressive effects of edema or subjected to long-term mechanisms of neurodegeneration and neuromodulation. It may progress over days, weeks, months or even years. Many different mechanisms play a role in its formation; necroptosis, apoptosis, excitotoxicity, oxidative stress, mitochondrial dysfunction, calcium overflow are some of them. It is often observed in the adjacent area of primary injury and seldom in remote areas. The belief that it can be partially limited or reversed has made secondary injury mechanisms the main focus of current researches.[7,8,10]

Delayed cell death is one of the main elements of secondary injury. It occurs either as a continuation of primary cell death, by necrosis; or in a planned manner, through apoptosis. Apoptosis is an active process which requires some amount of energy. During apoptosis, cell contents are first neatly packaged. These packages, called "apoptotic bodies", are then removed from the area by phagocytosis. Apoptosis does not trigger inflammation.[7,9]

In ischemic process, the most important factor that determines the fate of the cell is the amount of ATP (adenosine triphosphate) that can be produced. Energy-dependent ion-gated channels on the cell membrane cannot function in regions where ATP is insufficient or blood flow is severly impaired, which in turn cause necrosis. Apoptosis occur when ATP remains partially accessible for a period of time.[7-9]

2. Cellular Energy Insufficiency

Brain tissue can only tolerate lack of ATP for several minutes. So much so that approximately 5-10 minutes of total occlusion of artery is enough for irreversible tissue damage.[7]

Aerobic glycolysis is a series of reactions in which a net 36 ATP are synthesized from glucose. It consists of glycolysis, Krebs Cycle and ETS (electron transport system) phases. Oxygen is necessary for transportation of electrons in the ETS. If oxygen depletes, transport proteins and cytochromes remain reduced. Since there is no potential gradient, energy cannot be synthesized. In this case, anaerobic glycolysis comes into play to close the energy gap in the affected area and regenerate the idle NADH and FADH2.[11]

Anaerobic glycolysis is a series of reactions in which a net 2 ATP are synthesized from glucose. However, the energy obtained from this is far from sufficient to sustain cell life. In addition, accumulation of its end product, lactate, deepens acidosis in the cell and increases H+ ion toxicity.[12]

Moreover energy deficiency causes the ion gradient across the plasma membrane to detoriorate. Because most of the ATP synthesized by cell is used to operate ion-gated channels localized on the plasma membrane, which are responsible for maintenance of electrolyte and fluid balance. The Na-K ATPase pump in particular uses a significant portion of the energy reserve of a normal neuron.[13] If the Na-K ATPase pump does not work properly, the potassium kept inside by the pump leaves the cell while sodium, chloride and calcium ions held outside enters the cell, dragging water with them. This is called anoxic depolarization. Thus, cell swelling, which is the first stage of necrosis, occur.[14]

Another process where energy is required is maintaining calcium balance. A healthy cell tries to keep the amount inside citosol constant by both storing it in the endoplasmic reticulum and mitochondria and excreting the excess out of the cell with energy-dependent pumps. Maintaining this balance is crucial for the cell because calcium is responsible for the regulation of many enzyme activities.

In case of ischemia, calcium tends to accumulate intracellularly by various mechanisms. Some of these include Na-K ATPase dysfunction; exchangement of the increased Na+ and H+ ions with calcium by using Na+/Ca+2 regulator (NCX) and acid-sensitive ion channels (ASICs, which exchange Ca+2/H+).

Mitochondria, together with the endoplasmic reticulum, are important regulators of intracellular calcium balance. It stores calcium and magnesium via vesicles in its matrix. It also limits the amount of calcium entering its matrix via channels called "mitochondrial calcium uniporter (MCU)" which are localised on its inner membrane. This way, the amount of calcium mitochondria contain is kept constant. However, in case of energy insufficiency micro-connections are formed between the endoplasmic reticulum and mitochondria. This process is activated by excess calcium in the endoplasmic reticulum. These connections open closed MCU channels. As a result, excess calcium enters the mitochondria from the endoplasmic reticulum and cytosol. Mitochondria's calcium overload triggers apoptosis and swelling of the organelle and activation of destructive enzymes such as phospholipase, protease and endonuclease. All of these eventually disrupt the functioning of the organelle and lead to "lipid peroxidation".[7,14]

3. Excitatory Amino Acids

Glutamate is the main excitatory neurotransmitter of the adult central nervous system. Overstimulation of neurons with glutamate causes cell damage, as it is an excitotoxin. This damage is mostly mediated by calcium overload. Energy is required for synthesis and reuptake of neurotransmitters. In normal conditions, the amount of glutamate in synapses is tightly controlled by the synthesis-reabsorption cycle. When neuronal injury occurs, cell integrity is disrupted and excessive amounts of glutamate are released. Due to the accompanying ischemia, this excess glutamate also cannot be reabsorbed as all of these processes are energy dependent. Excess glutamate increases tissue damage by overstimulating the surrounding cells.[7,16]

Glutamate binds to two separate receptors that mediate the opening of ion channels in the plasma membrane. NMDAR (n-methyl-d-aspartate receptor) is the most striking among them, but AMPA/kainate (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) receptors also have an important role in the neurotoxic effect. In fact, activation of the AMPA channel plays a key role in the activation of the NMDA channel. AMPA receptor is an ionotropic receptor permeable to many ions, especially sodium. It has the ability to turn on and off quickly and it is responsible for rapid communication between neurons under routine conditions. It needs only the presence of glutamat to activate. When the amount of glutamate increases as a result of neuronal injury, excess glutamate bind to the AMPA receptors of neighboring cells. This results in opening of ion channels in AMPA which leads to Na+ influx and depolarisation. Activation of the AMPA receptor causes magnesium ions, which block NMDAR, to get released from the receptor.[15]

NMDAR is responsible for attention and learning in physiological process, as well as neurodegeneration in pathological process. For it to open under normal conditions, it must be separated from the magnesium ion to which it is bound.[17] Excess glutamate in the environment binds to the NMDA receptor, which is freed from magnesium by AMPA activation and fast depolarisation. Then intense amounts of calcium and sodium enter the cell through the opened channel. As previously explained, calcium overload ignites a series of enzyme cascades that result in cell damage.[15]

Activation of the NMDA receptor also stimulates nitric oxide production in the neuron. Nitric oxide is essentially a vasodilator neurotransmitter; but when synthesized in excess, it combines with superoxide and mediates the production of strong reactive oxygen radicals.[7,15]

4. Reperfusion Injury

Ensuring perfusion to the ischemic tissue quickly constitutes the basic treatment approach in acute stroke and is of vital importance in terms of saving as many cells as possible. However, these cells, which have been deprived of oxygen and nutrients for a certain period of time faces new threats when blood flow is restored. Rapid increase in concentration of oxygen in the tissue brings the potential for oxygen free radical formation. In addition, restoring circulation of the tissue where the blood-brain barrier is damaged, causes inflammatory cells to invade the area. All of these injuries that follow the restoration of blood flow are called "Reperfusion Injury" and have an extremely important role in the formation of secondary injury.[7]

Mitocondria plays an important role in progression of reperfusion injury. It has been proven that ischemia-reperfusion process causes post-translational changes in oxidative phosphorylation proteins. Thus, the mitochondrial membrane potential increases and therefore reactive oxygen radicals [Hydroxyl (OH), superoxide (O_2-) and peroxide (H_2O_2)] are synthesized. In addition, substrates of oxidative phosphorylation (AMP, xanthine, hypoxanthine) tend to accumulate during the ischemic process. When oxygen re-enters the cell, rapid use of these substrates releases reactive oxygen radicals. The cell membrane undergoes lipid peroxidation as a result of free radical damage.[18]

The role of immune mechanisms in reperfusion injury is still subject to current research. Previously, the central nervous system was thought to be relatively shielded from immune system thanks to low permeability of blood brain barrier (BBB). But current studies have shown that, during stroke, BBB is distrupted due to capillary endothelial injury during ischemia. Microglia are also activated by stress and secrete signaling proteins that mediate both inflammation and tissue repair. As reperfusion occurs, leukocytes responding to the call of microglia flood into the tissue across the damaged barrier. These leukocytes contribute to tissue damage by secreting cytokines such as "TNF, IL-1, IL-6". Additionally, platelets activated by these prosseses aggregate and adhere to the endothelium. Thus, perfusion further decreases and the damage worsens as the "PAF" secreted from those platelets also increases the damage. Clinical and laboratory trials have shown that neuroinflammation plays a role in acute damage as well as in long term tissue changes after damage.[7,18,31]

5. Abnormal Autoregulation, Vascular Reactivity, Chemoregulation

Optimal maintenance of brain functions depends on the continuity of cerebral blood flow. Under normal conditions, cerebral blood flow (CBF) is determined by the ratio of cerebral perfusion pressure (CPP) to cerebrovascular resistance (CVR). Cerebrovascular resistance depends on blood viscosity and vessel diameter. Mean cerebral perfusion pressure (mean CPP) is equal to the difference between the mean arterial blood pressure (MAP) in the cerebral circulation and venous pressure (ICP-intracranial pressure); which is normally around 90 mmHg.[2,22]

The brain's ability to maintain a constant level of CBF despite changes in CPP is called "autoregulation." Constant blood flow can be achieved while the MAP is in the range of 60-140 mmHg.[19] However, these numbers are not absolute and vary from person to person. It has been shown that the lower and upper limits of autoregulation increase in people with long-term hypertension. Thus, as tolerance to high blood pressure values increase, so does sensitivity to hypotension.[2]

An autoregulation example is as follows: cerebral perfusion pressure decreases, as in systemic hypotension or increased intracranial pressure. With the dilation of the precapillary vessels, cerebrovascular resistance decreases and cerebral blood flow remains constant. On the other hand, in case of hypertension, the vessels constrict. The resistance increases and the cerebral blood flow remains constant yet again.[2,22]

Baroreceptors are sensitive to changes in perfusion pressure. Although these receptors are found in the walls of all arteries, especially the arcus aorta, they are most

commonly located in the regions called "Carotid Sinus" located on the walls of both internal carotid arteries.[32]

When the mean arterial pressure drops below 60 mmHg, the expansion capacity of the precapillary vessels is exceeded. As a result, collapse occurs and CBF decreases. Therefore, any pathology that prevents the vessels' ability to dilate results in ischemia. Aforementioned pathologies include, but are not limited to, thrombus, embolism, vasospasm, neutrophil aggregation and tissue edema. When the mean arterial pressure exceeds 160 mmHg, the narrowing of the vessels reaches its highest level. As a result, hyperemia and vasogenic edema develop. As edema grows in size, healthy tissues are pushed to the sides, intracranial pressure increases, herniation symptoms occur. Vascular damage disrupts the vasoconstriction function, causing hyperperfusion and increased brain edema.[2,7,21,22]

Another aspect that affects the vascular wall diameter is the quantity of components that reflect the state of cell metabolism. These include the partial pressure of carbon dioxide, oxygen and the amount of H+ in the environment. This is called "chemoregulation". It is particularly noteworthy that the response to changes in carbon dioxide levels is rapid and potent. As $PaCO_2$ levels decrease, the vessels constrict; vessels dilate as $PaCO_2$ levels rise. Moreover, this effect remains intact unless a serious global damage occurs in the cerebrum. Since arterial circulation is interrupted in ischemic stroke, oxygen is consumed rapidly; PaO_2 levels decrease. As the produced CO_2 and H+ cannot be excreted from the tissue, their partial pressures keep rising. Hypercarbia caused by respiratory depression that may accompany ischemic stroke significantly increases cerebral blood flow. Excessive increase in cerebral blood flow causes cerebral edema. Therefore, in a stroke patient, it is of utmost importance to check breathing functions. If respiratory depression is present, it is vital to intubate the patient and ensure effective ventilation. On the other hand, hyperventilation to lower $PaCO_2$ causes rapid vasoconstriction and therefore decreases intracranial pressure. As a matter of fact, hyperventilation has long been used as a standard treatment protocol in patients with increased intracranial pressure. However, the harm of prolonged hyperventilation tends to outweigh its benefits. The primary harm being that it significantly reduces blood flow in sensitive vessels and triggers ischemia in these areas. Therefore, it is recommended to use the hyperventilation technique for a maximum of 4-6 hours before decompressive surgery or in emergency interventions.[2,19,20,24]

Response to oxygen level changes is slower, less dramatic. Vasodilation occurs when the oxygen level in the tissue drops below 50 mmHg.[19,20]

6. Increased Intracranial Pressure

In a normal adult, average intracranial pressure is 0-15 mmHg. In fact, transient intracranial pressure changes are common in a healthy individual. Sneezing, coughing, laughing, straining, and changes in head position all increase intracranial pressure, but since the pressure returns to normal in a short period of time, there are no major consequences. Intracranial hypertension is when the pressure exceeds 22 mmHg for more than 5 minutes.[2,7]

The cranium consists of 3 major components: brain tissue, cerebrospinal fluid (CSF) and blood. As explained in the Monroe-Kellie Doctrine, a slight increase in the volume of any of these three components is compensated by a decrease in the volume of the other two. Reasoning being that cranium is surrounded by a hard skull and has little to no ability to expand.[25]

In ischemic stroke, the increase in brain tissue volume is often secondary to abnormal fluid accumulation in the intracellular or interstitial space, which is called "cerebral edema". Cytotoxic edema is characterized by accumulation of water and sodium inside the cell, ultimately causing cell swelling. Whereas vasogenic edema occurs as a result of disruption of the blood-brain barrier which leads to extravasation of electrolytes, water, albumin and similar intravascular proteins into the interstitial space. Processes that increase intravascular pressure, damage the capillary wall or cause vasodilation increase vasogenic edema. These include severe hypertension, hypercarbia, stroke and fever. Cytotoxic edema is observed within the initial hours of ischemic stroke. Vasogenic edema presents itself as a delayed effect of secondary damage to the brain as it usually begins to develop within the first 2-3 days and peaks on the fifth day.[7,26]

Cerebral edema, when severe, initiates a cycle in which the pressure gradually increases and the condition becomes increasingly severe. As edema fluid accumulates, it narrows the local vessels and prevents sufficient blood and oxygen from reaching the cells. This will lead to ischemia, vasodilation, increased capillary pressure causing even more fluid to leak into the damaged tissue, thus increasing edema even further.[2,7]

The most undesirable consequence of cerebral edema and therefore increased intracranial pressure is the herniation of brain structures. The word "herniation" refers to the protrusion of brain tissue through an opening between the surrounding dura sheets. In particular, compression of important midline structures (reticular activator system, vital regulatory center) and brainstem is associated with rapid brain death if not treated immediately. During this process, there is a risk of compression of the arteries and development of secondary ischemia (such as compression of the anterior cerebral artery and pericallosal artery in Subfascinal Herniation).[27] In addition, a significant increase in intracranial pressure and compression of the vessels cause the activation of the sympathetic system to maintain brain perfusion which is named "Ischemic Response" or "Cushing's Triad" . Cushing's triad is considered as the brain's last effort to ensure perfusion.[7]

TREATMENT

Current treatment of acute ischemic stroke includes stabilizing vital functions, restoring perfusion in the salvageable penumbra tissue with endovascular and iv thrombolytic therapy and, if present, treating cerebral edema and the accompanying increased intracranial pressure. First and foremost, it is essential to ensure the patient's airway, breathing and circulation are in order. Then glucose is measured from the fingertip, hypo-hyperglycemia is quickly intervened. Electrolytes, blood count, coagulation parameters, kidney and liver function tests are requested. Hypertension seen in the acute phase of ischemic stroke is most likely the body's attempt to reduce tissue damage by increasing cerebral perfusion. Therefore, hypertension should not be treated untill blood pressure reaches or exceeds 220/120 mmHg. However, if thrombolytic is to be administered, blood pressure should be maintained below 185/110. Hypotension, however, should always be treated immediatly.[33]

Occurences such as pain and fever should be prevented as they will accelerate metabolism and increase energy consumption. Hyperosmolar agents such as hypertonic saline, mannitol draw water from the brain tissue, reducing intracranial pressure. Such agents are used in the treatment of vasogenic edema. Mannitol dosage is calculated based on the patient's weight. First, a bolus dose is given, then maintenance dose is repeated every 4-6 hours. The target osmolarity is 320 mOsm/L and the maintenance dose is adjusted according to the patient's response and blood test results. Treatment should be reduced gradually since sudden stoppage may cause rebound edema and patients may develop resistance to mannitol during long term usage.[27]

Hypertonic saline can be administired as a bolus or as a continuous infusion. The serum sodium target is below 160. In case of infusion, sodium levels should be monitored by taking blood samples every 4-6 hours and the dose should be adjusted accordingly.[7,27]

Decompressive surgery is a life-saving treatment for select patients, especially in the first 48 hours.

Hypothermia's (32-33°C) use in treatment-resistant CIBAS is being researched due to its metabolism-slowing effect. Although it has been shown to reduce intracranial pressure, its significance in regards to clinical outcomes has not yet been confirmed. Moreover, the therapeutic window of effect, duration of application, safe rewarming protocols have not been fully defined. In addition, the shivering that occurs as a result of hypothermia neutralizes the positive effect of the treatment by increasing the oxygen demand in the tissue. Therefore more studies are required before hypothermia can be used reliably in the treatment of ischemic stroke.[7,28]

Finally, barbiturate coma may be attempted when all preceding options have failed. Pentobarbital infusion reduces cerebral metabolism while increasing membrane stabilization. The major downside of barbiturate coma is the inability to perform a neurological examination. Moreover hypotension is a common side effect in these patients.[7,29]

CONCLUSION

Ischemic stroke is an acute disease with high morbiditiy and mortality rates all around the globe. However, current studies come up short in many aspects. Current treatment algoritm only serves to preserve the penumbra tissue as much as possible in select patients, while aiming to limit secondary injury. Better understanding the pathophysiology of ischemia will not only open up new treatment options, but it may also help us understand the posibilities of reversing tissue damage. Studies conducted in the following years will both shed light on unanswered questions regarding the mechanism of the disease and reshape the treatment algorithm.

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Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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