



PATHOGENESIS AND MORPHOLOGY OF ISCHEMIC STROKE: MODERN PERSPECTIVES

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***Abstract** This article analyzes the modern mechanisms of ischemic stroke pathogenesis and morphological changes. Ischemic stroke remains one of the leading causes of death and disability worldwide. The article covers the interrelationship of excitotoxicity, oxidative stress, inflammation, and apoptosis processes, as well as the significance of the penumbra zone. The clinical correlation of morphological changes and modern diagnostic possibilities are reviewed.*

***Keywords:** ischemic stroke, pathogenesis, penumbra, neuron, apoptosis, morphology*

INTRODUCTION

Stroke (cerebrovascular accident) is the second leading cause of death and disability worldwide. According to the World Health Organization, 15 million people suffer from stroke annually, of which 5 million die and another 5 million remain permanently disabled. Ischemic stroke accounts for 80-85% of all stroke cases [1]. Ischemic stroke occurs as a result of acute disturbance of cerebral circulation and is characterized by a sharp decrease in the supply of oxygen and glucose to neurons. In recent years, significant advances have been made in understanding the molecular mechanisms of ischemic stroke pathogenesis, which has enabled the development of new therapeutic strategies [2]. The purpose of this article is to analyze the modern mechanisms of ischemic stroke pathogenesis and the morphological changes occurring in brain tissue.

MAIN MECHANISMS OF ISCHEMIC STROKE PATHOGENESIS

The pathogenesis of ischemic stroke is a complex and multi-stage process, encompassing several closely interrelated mechanisms. According to the integrative

model proposed by Dirnagl et al. (1999), the ischemic cascade includes the following stages: energy deficiency, excitotoxicity, oxidative stress, inflammation, and apoptosis [3].

Energy Deficiency and Disruption of Ion Homeostasis

When cerebral blood flow stops, within seconds the reserves of oxygen and glucose in neurons are depleted. As a result, ATP synthesis sharply decreases, and the cell enters a state of energy deficiency. Due to ATP deficiency, the activity of Na⁺/K⁺-ATPase (sodium-potassium pump) is disrupted, leading to changes in the ion gradient. Na⁺, Ca²⁺, and water enter the cell, while K⁺ exits the cell. This process leads to cellular swelling (cytotoxic edema) [4].

Excitotoxicity

Excitotoxicity is one of the central mechanisms in the pathogenesis of ischemic stroke. Under ischemic conditions, glutamate—the main excitatory neurotransmitter—accumulates excessively in the synaptic space. This occurs due to several reasons:

- glutamate reuptake is disrupted due to energy deficiency;
- vesicular and non-vesicular release of glutamate increases due to depolarization;
- astrocytic glutamate transport is inhibited [5].

Excessive accumulation of glutamate leads to overactivation of NMDA and AMPA receptors. This causes an excessive influx of Ca²⁺ into the cell. Increased Ca²⁺ concentration in the cytosol and mitochondria triggers a series of damaging processes: activation of phospholipases, proteases, and nucleases, mitochondrial dysfunction, and formation of free radicals [3, 5].

Oxidative Stress

During ischemia and especially during reperfusion, free radicals—superoxide (O₂⁻), hydrogen peroxide (H₂O₂), and hydroxyl radical (OH⁻)—are produced in large

quantities. This process is called "oxidative stress". The main sources of free radicals are:

- disruption of the mitochondrial electron transport chain;
- activation of xanthine oxidase enzyme;
- activation of inflammatory cells (neutrophils, microglia);
- increased metabolism of arachidonic acid [6].

Free radicals cause peroxidation of lipids in cell membranes, oxidation of proteins, and damage to DNA. Particularly, polyunsaturated fatty acids in neuronal membranes are highly susceptible to oxidative damage. This process disrupts the integrity of cell membranes and leads to neuronal death [7].

Inflammatory Response

Following ischemia, a rapidly developing inflammatory response in brain tissue is an important component of pathogenesis. Several hours after ischemia, microglia (the resident macrophages of the brain) become activated and produce pro-inflammatory cytokines—interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) [8]. Subsequently, due to increased permeability of the blood-brain barrier, leukocytes (neutrophils, followed later by monocytes and lymphocytes) infiltrate the brain tissue. Proteolytic enzymes and free radicals produced by leukocytes exacerbate tissue damage. Modern research shows that the inflammatory process plays a dual role: while it has damaging effects in the initial stages, it may contribute to tissue repair in later reparative stages [2, 8].

Apoptosis and Necrosis

In ischemic stroke, neuronal death occurs through two main mechanisms—necrosis and apoptosis. In the infarct core (central zone), where blood flow is most severely reduced (below 10-15 ml/100 g/min), necrosis predominates. Necrosis is characterized by cell swelling, membrane rupture, and inflammation [9]. In the penumbra zone (blood flow 20-40 ml/100 g/min), the apoptosis mechanism predominates. Apoptosis—programmed cell death—is an energy-requiring process.

In apoptosis, the caspase cascade is activated, DNA undergoes fragmentation, and the cell shrinks and divides into apoptotic bodies. Apoptotic cells are cleared through phagocytosis, and no inflammatory response is observed [9, 10].

Studies conducted by Bunting et al. (2022) have shown that the integrity of the neurovascular unit (neurons, endothelial cells, pericytes, astrocytes, and basal membrane) plays an important role in stroke pathogenesis. Damage to the neurovascular unit leads to disruption of the blood-brain barrier and secondary damage [2].

PENUMBRA ZONE - THERAPEUTIC TARGET

The concept of the penumbra zone was first introduced by Astrup et al. (1981). The penumbra is an area where blood flow is below the critical level, but cells still maintain vital activity. In this zone, neurons have lost electrical activity, but ion homeostasis and energy metabolism are partially preserved [11].

Characteristics of the penumbra zone:

- blood flow is around 20-40 ml/100 g/min (normally 50-60 ml/100 g/min);
- cells are relatively preserved morphologically;
- functional activity is lost, but structural integrity is maintained;
- metabolic disturbances are reversible in nature;
- over time (hours, sometimes days), this zone may transform into the infarct core [11, 12].

The penumbra zone is the main target of modern stroke therapy. It is by preserving neurons in this zone that the consequences of stroke can be reduced. Therefore, based on the principle that "time is brain," thrombolytic therapy (tissue plasminogen activator - tPA) and mechanical thrombectomy should be performed as quickly as possible [2].

In recent studies conducted by Liu et al. (2026), the possibilities of restoring the microenvironment in the infarct core and penumbra zone using neutrophil-mimetic "nanobuffer" technology have been investigated. This approach helps

protect neurons in the penumbra zone by reducing inflammation and oxidative stress [12].

MORPHOLOGICAL CHANGES IN ISCHEMIC STROKE

Morphological changes occurring in brain tissue during ischemic stroke develop in stages over time. According to "Greenfield's Neuropathology" (10th edition, 2025), these changes can be observed at both macroscopic and microscopic levels [13].

Macroscopic Changes

Early stage (12-24 hours): During the first 6-12 hours, macroscopic changes may not be noticeable. After 12-24 hours, color changes (pallor) and softening of tissue consistency are observed in the affected area. Brain tissue swelling occurs, which can lead to deformity of sulci and ventricles [13].

2-3 days: The infarct zone becomes clearly demarcated, taking on a yellowish-gray color. Tissue swelling increases, which increases the risk of brain herniation (dislocation syndrome).

7-10 days: The infarct zone softens and acquires a gelatinous consistency. Borders are clear, color is yellowish-gray.

2-3 weeks: As necrotic masses are resorbed and liquefied, a cyst (cavity) begins to form.

Several months: In the final stage, a fluid-filled cyst or glial scar is formed [13, 14].

Microscopic Changes

Microscopic changes in neurons during ischemic stroke have characteristic features.

Ischemic neuronal change ("red neuron"): 6-12 hours after ischemia, eosinophilic staining of the cytoplasm (acidophilia) and pyknosis (shrinkage and darkening) of the nucleus are observed in neurons. This sign is called the "red neuron" and is a characteristic morphological feature of ischemic damage [13].

Neuronophagia: The process of necrotic neurons being engulfed by microglia and phagocytes. This phenomenon usually begins 24-48 hours after ischemia.

Vacuolization: The appearance of vacuoles in the cytoplasm, associated with damage to mitochondria and endoplasmic reticulum.

Glial cell reaction:

- Microglia: Become activated, proliferate, and perform phagocytic function.

Detected using microglial markers (Iba-1, CD68).

- Astroglia: Reactive astrocytes swell, proliferate, and GFAP (glial fibrillary acidic protein) expression increases. Astrocytes participate in the formation of glial scars [13, 15].

Myelin changes: The demyelination process is characterized by the breakdown of the myelin sheath in the ischemic zone. This is detected using Luxol fast blue or immunohistochemical markers (MBP - myelin basic protein).

Vascular changes: Damage to endothelial cells, disruption of the blood-brain barrier, perivascular edema, and in some cases, diapedesis hemorrhages are observed [15]

CLINICAL-MORPHOLOGICAL CORRELATION

The clinical presentation of ischemic stroke depends on which blood vessel is affected. The most common localizations:

Middle Cerebral Artery (MCA) Territory (50-70% of cases)

- Damage: motor and sensory cortex, Broca's and Wernicke's areas
- Clinical signs: contralateral hemiparesis and hemihypesthesia (more pronounced in face and arm), aphasia (when left hemisphere is affected), anosognosia (when right hemisphere is affected)

Anterior Cerebral Artery (ACA) Territory (3-5% of cases)

- Damage: motor cortex leg representation, supplementary sensorimotor area
- Clinical signs: contralateral monoparesis (leg), urinary incontinence, abulia

Posterior Cerebral Artery (PCA) Territory (10-15% of cases)

- Damage: occipital lobe, thalamus, mesencephalon
- Clinical signs: contralateral homonymous hemianopia, thalamic syndrome, oculomotor disturbances

Vertebrobasilar Territory (20% of cases)

- Damage: brainstem, cerebellum
- Clinical signs: dizziness, diplopia, dysarthria, dysphagia, ataxia, "crossed" syndromes [14, 16]

MODERN DIAGNOSTICS AND MARKERS

Modern immunohistochemical and neuroimaging methods play an important role in the diagnosis of ischemic stroke and determination of prognosis. Immunohistochemical Markers:

- Neuronal markers: NeuN (normal neurons), MAP2 (damaged neurons)
- Apoptosis markers: Caspase-3, TUNEL
- Gliosis markers: GFAP (astrocytes), Iba-1, CD68 (microglia)
- Oxidative stress markers: 4-HNE, 8-OHdG
- Inflammation markers: IL-1 β , TNF- α , COX-2 [15, 17]

Neuroimaging:

- CT (computed tomography): Detection of hyperacute changes in the early stage is limited, but important for excluding hemorrhage
- MRI (magnetic resonance imaging): Diffusion-weighted imaging (DWI) shows changes within hours after ischemia
- Perfusion CT/MRI: Important for detecting the penumbra zone - "image or perfusion core" mismatch serves as a criterion for thrombolytic therapy
- Angiography: Gold standard for detecting vascular occlusion [2, 16]

CONCLUSION

The pathogenesis of ischemic stroke is a complex and multifactorial process, encompassing mechanisms such as energy deficiency, excitotoxicity, oxidative

stress, inflammation, and programmed cell death. The penumbra zone—the salvageable area around the infarct core—is the main target of modern therapy.

Morphological changes in ischemic stroke develop in stages over time: initially "red neuron" type changes in neurons, followed by neuronophagia, glial reaction, and finally cyst formation or glial scarring. Modern immunohistochemical markers and neuroimaging methods are crucial for stroke diagnosis, prognosis, and selection of treatment strategy.

Deep understanding of pathogenic mechanisms enables the development of new therapeutic approaches. Neuroprotective strategies, modulation of inflammation, reduction of oxidative stress, and regenerative medicine methods may form the basis of future stroke therapy.

REFERENCES

1. World Health Organization. Global Health Estimates 2020: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2019. Geneva: WHO; 2020.
2. Tiedt S, Buchan AM, Dichgans M, et al. The neurovascular unit and systemic biology in stroke—implications for translation and treatment. *Nature Reviews Neurology*. 2022;18:597-612.
3. Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. *Trends in Neurosciences*. 1999;22(9):391-397.
4. Lo EH, Dalkara T, Moskowitz MA. Mechanisms, challenges and opportunities in stroke. *Nature Reviews Neuroscience*. 2003;4(5):399-415.
5. Lai TW, Zhang S, Wang YT. Excitotoxicity and stroke: identifying novel targets for neuroprotection. *Progress in Neurobiology*. 2014;115:157-188.
6. Shirley R, Ord EN, Work LM. Oxidative stress and the use of antioxidants in stroke. *Antioxidants*. 2014;3(3):472-501.
7. Yuchun Wang, et al. Metabolic reprogramming in ischemic stroke: when glycolytic overdrive meets lipid storm. *Cell Death & Disease*. 2025;16:45-58.

8. Iadecola C, Anrather J. The immunology of stroke: from mechanisms to translation. *Nature Medicine*. 2011;17(7):796-808.
9. Broughton BR, Reutens DC, Sobey CG. Apoptotic mechanisms after cerebral ischemia. *Stroke*. 2009;40(5):e331-e339.
10. Radak D, Katsiki N, Resanovic I, et al. Apoptosis and acute brain ischemia in ischemic stroke. *Current Vascular Pharmacology*. 2017;15(2):115-122.
11. Astrup J, Siesjö BK, Symon L. Thresholds in cerebral ischemia - the ischemic penumbra. *Stroke*. 1981;12(6):723-725.
12. Shanshan Liu, Jianpei Xu, Yipu Liu, et al. Neutrophil-Biomimetic "Nanobuffer" for Remodeling the Microenvironment in the Infarct Core and Protecting Neurons in the Penumbra. *ACS Applied Materials & Interfaces*. 2026;18(3):1123-1138.
13. Love S, Perry A, Ironside J, Budka H. *Greenfield's Neuropathology*. 10th ed. CRC Press; 2025.
14. Kumar V, Abbas AK, Aster JC. *Robbins & Cotran Pathologic Basis of Disease*. 10th ed. Philadelphia: Elsevier; 2020.
15. Zhang Y, et al. Microglial activation in ischemic stroke: a review. *Neurochemistry International*. 2021;145:105012.
16. Caplan LR. *Caplan's Stroke: A Clinical Approach*. 5th ed. Cambridge University Press; 2016.
17. Abzalova S., Kaldibaeva A. Early morphological changes in the liver under experimental cerebral ischemic stroke conditions. *Tashkent Pediatric Medical Institute Scientific Works*. 2013;2:45-48.