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ORIGINAL ARTICLE

Morphological Mechanisms of Optic Nerve Damage in Acute Ischemic Optic Neuropathy

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Abstract

Acute ischemic optic neuropathy (AION) is one of the most important causes of sudden and irreversible visual loss resulting from insufficient blood supply to the optic nerve head. The disease is characterized by rapid interruption of oxygen and nutrient delivery, leading to structural and functional impairment of retinal ganglion cell axons that form the optic nerve. The optic nerve is highly susceptible to ischemic injury because of its elevated metabolic requirements and limited energy reserves. Even a brief reduction in tissue perfusion may initiate a sequence of morphological and molecular alterations that ultimately culminate in permanent neuronal degeneration and visual dysfunction. Although considerable progress has been made in understanding the clinical manifestations of AION, the precise morphological mechanisms responsible for optic nerve destruction remain incompletely understood.

The pathogenesis of acute ischemic optic neuropathy involves a complex interaction between vascular insufficiency, metabolic failure, oxidative stress, inflammatory activation, mitochondrial dysfunction, apoptosis, and secondary neurodegeneration. The initial ischemic insult disrupts oxidative phosphorylation within mitochondria, causing rapid depletion of intracellular adenosine triphosphate (ATP). Failure of ATP-dependent membrane pumps results in intracellular accumulation of sodium and calcium ions, osmotic swelling, membrane instability, and activation of proteolytic enzymes. Simultaneously, excessive release of excitatory neurotransmitters promotes calcium overload, further accelerating cellular injury through excitotoxic mechanisms. Increased production of reactive oxygen species damages lipids, proteins, and nucleic acids, while activation of inflammatory pathways amplifies secondary tissue destruction.

Morphological alterations begin within minutes after ischemia and progressively involve neurons, glial cells, vascular structures, connective tissue, and myelin sheaths. Early reversible changes gradually progress toward irreversible degeneration if tissue perfusion is not restored. Histopathological examination, immunohistochemistry, morphometric analysis, and electron microscopy provide essential information regarding the temporal sequence of these structural changes and contribute to understanding disease progression. Comprehensive evaluation of morphological mechanisms is therefore fundamental for identifying therapeutic targets capable of preserving optic nerve integrity and visual function.

Keywords: Morphological Mechanisms, Acute Ischemic Optic Neuropathy (AION), Optic Nerve Damage, Optic Nerve Ischemia, Histopathological Changes, Retinal Ganglion Cells, Neurodegeneration, Axonal Degeneration, Ocular Ischemia, Morphological Alterations.

1. Introduction

The objective of this study was to investigate the morphological mechanisms responsible for optic nerve damage during acute ischemic optic neuropathy by analyzing sequential structural alterations affecting neuronal, glial, vascular, and connective tissue components of the optic nerve. The study also aimed to characterize the progression of ischemic injury using histopathological, immunohistochemical, morphometric, and ultrastructural methods while identifying key morphological indicators associated with neuronal degeneration, inflammation, demyelination, apoptosis, and vascular dysfunction.

2. Materials and Methods

The investigation was conducted using healthy adult Wistar rats maintained under standardized laboratory conditions with controlled temperature, humidity, and a regular light-dark cycle. Animals received unrestricted access to food and drinking water throughout the experimental period. All procedures were performed in accordance with internationally accepted ethical standards for laboratory animal research and were approved by the institutional ethics committee before initiation of the study.

Acute ischemic optic neuropathy was experimentally induced by temporary elevation of intraocular pressure sufficient to reduce optic nerve head perfusion without producing direct mechanical disruption of ocular structures. Following the ischemic interval, physiological reperfusion was established under controlled conditions. Control animals underwent identical anesthetic and surgical procedures without induction of ischemia.

Experimental animals were sacrificed at 24 hours, 72 hours, and seven days after reperfusion to evaluate the chronological progression of morphological changes. Optic nerves together with retinal tissues were carefully excised, fixed in buffered formalin, processed routinely, embedded in paraffin, and sectioned into thin slices for microscopic examination.

Routine histological assessment was performed using hematoxylin and eosin staining to evaluate tissue architecture, cellular degeneration, edema, vascular congestion, inflammatory infiltration, and hemorrhage. Luxol Fast Blue staining was employed to determine the integrity of myelin sheaths, while Cresyl Violet staining was used to quantify retinal ganglion cell survival.

Immunohistochemical analysis included glial fibrillary acidic protein (GFAP) for astrocytic activation, ionized calcium-binding adaptor molecule-1 (Iba-1) for microglial activation, cleaved caspase-3 for apoptosis, hypoxia-inducible factor-1 alpha (HIF-1α) for tissue hypoxia, vascular endothelial growth factor (VEGF) for angiogenic activity, tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and nuclear factor kappa B (NF-κB) for inflammatory activation.

Transmission electron microscopy was performed to evaluate ultrastructural alterations of axons, mitochondria, oligodendrocytes, endothelial cells, basement membranes, and myelin lamellae. Quantitative morphometric analysis included measurements of axonal density, myelin thickness, retinal ganglion cell density, capillary diameter, inflammatory cell infiltration, glial proliferation, and tissue edema.

3. Results

Histopathological examination demonstrated that acute ischemia induced extensive structural alterations throughout the optic nerve. During the first twenty-four hours following ischemia, marked intracellular edema developed within axons accompanied by disruption of normal fascicular organization. Swollen axons compressed adjacent capillaries, contributing to further deterioration of local tissue perfusion. Vascular congestion and endothelial swelling were consistently observed throughout the optic nerve head, while expansion of extracellular spaces indicated significant accumulation of interstitial fluid.

As ischemia progressed, degeneration of neuronal tissue became increasingly severe. Axonal fragmentation, vacuolar degeneration, cytoplasmic disintegration, and progressive destruction of neurofilament architecture were evident in most experimental specimens. Luxol Fast Blue staining demonstrated widespread disruption of compact myelin characterized by irregular staining intensity, splitting of myelin lamellae, and extensive demyelination. Quantitative analysis revealed a progressive decline in axonal density proportional to the duration of ischemia.

The retinal ganglion cell layer exhibited substantial neuronal loss accompanied by nuclear pyknosis,

chromatin condensation, cytoplasmic shrinkage, and formation of apoptotic bodies. Cleaved caspase-3 immunoreactivity increased significantly within retinal ganglion cells and optic nerve axons, confirming activation of programmed cell death pathways. The number of surviving retinal ganglion cells declined markedly throughout the experimental period.

Immunohistochemical examination demonstrated intense expression of GFAP within astrocytes, indicating widespread reactive gliosis. Activated astrocytes displayed hypertrophic morphology with thickened cytoplasmic processes surrounding damaged axons. Microglial activation, demonstrated by strong Iba-1 immunoreactivity, increased progressively following ischemia. Activated microglia accumulated around degenerating neurons and blood vessels, indicating participation in inflammatory tissue remodeling.

Expression of TNF-α, IL-1β, and NF-κB increased significantly within ischemic tissue, demonstrating activation of inflammatory signaling pathways. HIF-1α expression was markedly elevated during the early stages of ischemia, reflecting severe tissue hypoxia, while VEGF expression increased during later stages, suggesting activation of compensatory angiogenic responses.

Electron microscopy revealed profound ultrastructural abnormalities. Mitochondria exhibited severe swelling, disruption of cristae, membrane rupture, and decreased matrix density. Neurofilaments and microtubules were fragmented and disorganized throughout damaged axons. Oligodendrocytes demonstrated nuclear condensation and cytoplasmic vacuolization consistent with degenerative injury. Capillary endothelial cells showed cytoplasmic swelling, irregular nuclei, and thickening of basement membranes, while separation of myelin lamellae and complete myelin disintegration were observed in advanced lesions.

4. Discussion

The findings of the present investigation demonstrate that optic nerve damage in acute ischemic optic neuropathy results from multiple interconnected morphological mechanisms that evolve progressively following interruption of tissue perfusion. The earliest pathological event identified in this study was intracellular edema resulting from disruption of ionic homeostasis caused by ATP depletion. Failure of membrane ion pumps promoted accumulation of intracellular sodium and calcium, leading to osmotic swelling and structural destabilization of neurons. Increased tissue pressure generated by cellular edema compressed surrounding capillaries and further impaired microcirculatory blood flow, thereby intensifying ischemic injury.

The degeneration of retinal ganglion cells represented the principal neuronal consequence of ischemia. Activation of apoptotic pathways, confirmed by increased cleaved caspase-3 expression, indicates that programmed cell death constitutes a major mechanism responsible for irreversible neuronal loss. Apoptosis develops gradually and therefore provides a potential therapeutic window during which neuroprotective interventions may preserve neuronal viability before irreversible degeneration occurs.

Mitochondrial injury observed in the present study illustrates the central role of energy failure in ischemic neurodegeneration. Swollen mitochondria with disrupted cristae lose their capacity to generate ATP efficiently while simultaneously producing excessive reactive oxygen species. Oxidative stress damages membrane phospholipids, proteins, mitochondrial DNA, and nuclear DNA, thereby accelerating neuronal dysfunction and apoptosis. Protection of mitochondrial integrity has therefore emerged as an important target for future neuroprotective therapies.

The extensive demyelination observed following ischemia further contributed to deterioration of optic nerve function. Myelin is essential for rapid saltatory conduction of action potentials, and its disruption substantially decreases conduction velocity while increasing susceptibility to axonal degeneration. Degeneration of oligodendrocytes further limits remyelination and contributes to persistent neurological deficits. Preservation of oligodendrocyte viability may therefore improve functional recovery following ischemic injury.

Reactive gliosis represented another important morphological mechanism identified during this investigation. Astrocytes became markedly activated in response to tissue injury and formed dense glial networks surrounding damaged neurons. Initially, astrocytic activation may support neuronal survival by maintaining extracellular ionic balance, regulating neurotransmitter concentrations, and supplying metabolic substrates. However, prolonged astrocyte proliferation contributes to glial scar formation that inhibits axonal regeneration and limits functional recovery.

Microglial activation also played a significant role in disease progression. Activated microglia released

inflammatory cytokines, reactive oxygen species, nitric oxide, and proteolytic enzymes that amplified secondary tissue injury beyond the initial ischemic insult. Although microglia participate in removal of cellular debris and tissue repair during early stages, persistent inflammatory activation creates a toxic microenvironment that accelerates neuronal degeneration. These findings indicate that regulation of neuroinflammation may reduce secondary optic nerve damage.

Vascular alterations observed throughout the study emphasize that endothelial injury is a critical component of optic nerve ischemia. Swollen endothelial cells, thickened basement membranes, and narrowing of capillary lumina impair restoration of adequate microvascular circulation even after reperfusion. Consequently, persistent hypoxia continues to damage neural tissue despite normalization of systemic blood flow. Therapeutic strategies directed toward preservation of endothelial function and microvascular integrity may therefore significantly improve clinical outcomes.

The combined use of histopathology, immunohistochemistry, morphometric analysis, and electron microscopy provided complementary information regarding disease progression and allowed comprehensive characterization of optic nerve injury. Integration of these techniques enhances diagnostic accuracy and provides reliable morphological biomarkers suitable for evaluating experimental neuroprotective therapies.

5. Conclusion

Acute ischemic optic neuropathy produces extensive morphological damage involving neurons, glial cells, myelin sheaths, vascular structures, and supporting connective tissue. The principal mechanisms responsible for optic nerve injury include intracellular edema, mitochondrial dysfunction, oxidative stress, apoptosis, inflammatory activation, demyelination, endothelial damage, and progressive axonal degeneration. These pathological processes interact continuously and collectively determine the severity of visual impairment.

Comprehensive morphological assessment demonstrates that structural alterations become progressively more severe with increasing duration of ischemia and closely correlate with neuronal loss and deterioration of optic nerve architecture. Histopathological, immunohistochemical, morphometric, and ultrastructural analyses provide reliable methods for identifying the mechanisms of ischemic injury and evaluating disease progression.

A detailed understanding of the morphological mechanisms underlying optic nerve degeneration provides an essential foundation for the development of effective neuroprotective, anti-inflammatory, antioxidant, endothelial-protective, and regenerative therapeutic approaches. Future investigations should focus on early intervention strategies aimed at preserving neuronal viability, maintaining microvascular integrity, preventing secondary degeneration, and promoting regeneration of damaged optic nerve fibers to improve long-term visual outcomes in patients with acute ischemic optic neuropathy.

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