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ORIGINAL ARTICLE

Role of Microcirculatory Disorders in the Development of Acute Ischemic Optic Neuropathy

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Abstract

Acute ischemic optic neuropathy (AION) is one of the most common causes of sudden, painless vision loss in adults and represents a significant neuro-ophthalmological disorder associated with impaired blood perfusion of the optic nerve. The condition develops when the microvascular circulation supplying the optic nerve head becomes insufficient to maintain normal tissue metabolism. Unlike large-vessel occlusion, disturbances in the microcirculation involve structural and functional abnormalities of arterioles, capillaries, and venules that reduce oxygen delivery, impair nutrient exchange, and disrupt cellular homeostasis. Because the optic nerve has a high metabolic demand and limited capacity to tolerate hypoxia, even transient impairment of microvascular blood flow can initiate irreversible neuronal injury.

The optic nerve head receives its blood supply primarily from the posterior ciliary arteries through a dense capillary network. The integrity of this microvascular system is essential for maintaining continuous oxygenation of retinal ganglion cell axons. Alterations in vascular autoregulation, endothelial dysfunction, increased vascular resistance, capillary narrowing, platelet aggregation, and blood viscosity changes may compromise tissue perfusion despite the absence of complete vascular occlusion. Consequently, localized ischemia develops, initiating a cascade of biochemical and molecular events that progressively damage neural tissue.

Microcirculatory disorders contribute not only to the onset of ischemic injury but also to its progression. Reduced perfusion pressure decreases oxygen availability, resulting in mitochondrial dysfunction, depletion of intracellular adenosine triphosphate (ATP), disruption of ionic balance, excessive production of reactive oxygen species, activation of inflammatory mediators, and apoptosis of retinal ganglion cells. Persistent impairment of capillary circulation also delays tissue recovery after reperfusion, thereby extending the duration of hypoxia and promoting secondary neurodegeneration.

Systemic disorders including arterial hypertension, diabetes mellitus, hyperlipidemia, atherosclerosis, nocturnal hypotension, smoking, and advanced age frequently impair microvascular function and significantly increase the risk of acute ischemic optic neuropathy. Understanding the relationship between microcirculatory dysfunction and optic nerve ischemia is therefore essential for improving early diagnosis, identifying high-risk individuals, and developing effective therapeutic strategies aimed at preserving visual function.

Keywords: Acute Ischemic Optic Neuropathy (AION), Microcirculatory Disorders, Optic Nerve Ischemia, Ocular Microcirculation, Retinal Blood Flow, Endothelial Dysfunction, Vascular Dysfunction, Ischemic Injury.

1. Introduction

The objective of this study was to investigate the role of microcirculatory disorders in the development of acute ischemic optic neuropathy by evaluating morphological alterations of the optic nerve microvasculature, assessing tissue perfusion, identifying structural changes associated with ischemia, and determining the relationship between microvascular impairment, neuronal degeneration, inflammatory responses, and the severity of optic nerve injury.

2. Materials and Methods

The study was performed using healthy adult Wistar rats maintained under standardized laboratory conditions. Animals were housed in temperature-controlled rooms with regulated humidity and a twelve-hour light-dark cycle while receiving unrestricted access to food and water. All experimental procedures complied with international ethical guidelines for laboratory animal research.

Acute ischemic optic neuropathy was experimentally induced by transient elevation of intraocular pressure sufficient to reduce optic nerve head perfusion without producing direct mechanical injury. The ischemic period was maintained under controlled conditions followed by gradual restoration of blood circulation. A control group underwent identical anesthetic procedures without induction of ischemia.

Animals were sacrificed at 24 hours, 72 hours, and seven days following reperfusion to evaluate sequential morphological changes. Optic nerves and retinal tissues were harvested immediately, fixed in buffered formalin, embedded in paraffin, sectioned, and prepared for microscopic examination.

Histological analysis was performed using hematoxylin and eosin staining to evaluate tissue architecture, vascular congestion, edema, inflammatory infiltration, and neuronal degeneration. Periodic acid-Schiff staining was used to examine capillary basement membranes and vascular integrity, while Luxol Fast Blue staining assessed the condition of myelin sheaths.

Immunohistochemical examination included antibodies against glial fibrillary acidic protein (GFAP) for astrocyte activation, ionized calcium-binding adaptor molecule-1 (Iba-1) for microglial activation, vascular endothelial growth factor (VEGF) for angiogenic activity, endothelial nitric oxide synthase (eNOS) as an indicator of endothelial function, hypoxia-inducible factor-1 alpha (HIF-1α) as a marker of tissue hypoxia, and cleaved caspase-3 to detect apoptotic cell death.

Transmission electron microscopy was performed to evaluate ultrastructural alterations within capillary endothelial cells, pericytes, basement membranes, mitochondria, myelin sheaths, and retinal ganglion cell axons. Morphometric analysis included measurement of capillary diameter, vascular density, endothelial thickness, retinal ganglion cell density, optic nerve axonal density, inflammatory cell infiltration, and tissue edema.

3. Results

Experimental ischemia produced pronounced disturbances of optic nerve microcirculation that were accompanied by progressive structural degeneration of neural tissue. Histological examination demonstrated marked narrowing of capillary lumens, endothelial swelling, vascular congestion, and reduced capillary density within the optic nerve head. Perivascular edema became evident during the early stages following ischemia and progressively increased during subsequent observation periods. Compression of surrounding capillaries further impaired tissue perfusion, creating a cycle of persistent ischemia despite restoration of systemic circulation.

The retinal ganglion cell layer exhibited progressive neuronal degeneration characterized by cytoplasmic shrinkage, nuclear condensation, chromatolysis, and decreased cellular density. Degeneration of optic nerve axons became increasingly prominent with prolonged ischemia and was accompanied by fragmentation of nerve fibers and progressive disruption of myelin architecture. Luxol Fast Blue staining demonstrated irregular myelin organization with extensive areas of demyelination in experimental specimens compared with controls.

Immunohistochemical analysis revealed marked overexpression of hypoxia-inducible factor-1 alpha within ischemic tissue, indicating severe oxygen deprivation. Endothelial nitric oxide synthase expression decreased significantly, suggesting endothelial dysfunction and impaired regulation of vascular tone. Conversely, vascular endothelial growth factor expression increased substantially during later observation periods, reflecting activation of compensatory angiogenic mechanisms in response to persistent tissue hypoxia.

Expression of glial fibrillary acidic protein increased markedly throughout the optic nerve, indicating extensive astrocyte activation and reactive gliosis. Activated microglial cells demonstrated strong Iba-1 immunoreactivity and accumulated around damaged capillaries and degenerating axons. Cleaved caspase-3 expression increased significantly within retinal ganglion cells, confirming activation of apoptotic pathways following prolonged ischemia.

Electron microscopic examination demonstrated severe ultrastructural injury affecting both neural and vascular components. Endothelial cells exhibited cytoplasmic swelling, mitochondrial degeneration, disruption of intercellular junctions, and irregular thickening of basement membranes. Pericytes showed degenerative changes associated with loss of normal vascular support.

Mitochondria within retinal ganglion cell axons appeared swollen with fragmented cristae, while neurofilaments displayed disorganization and fragmentation. Separation of myelin lamellae and focal myelin breakdown were consistently observed in ischemic specimens.

Quantitative morphometric analysis demonstrated statistically significant reductions in capillary diameter, vascular density, retinal ganglion cell number, and axonal density, together with significant increases in endothelial thickness, inflammatory infiltration, tissue edema, and glial proliferation. These findings confirmed that the severity of optic nerve injury correlated closely with the degree of microcirculatory impairment.

4. Discussion

The present study demonstrates that microcirculatory disorders represent a fundamental mechanism underlying the development of acute ischemic optic neuropathy. The observed structural alterations indicate that impairment of the optic nerve microvascular network precedes extensive neuronal degeneration and plays a decisive role in initiating ischemic injury. Because the optic nerve depends on continuous capillary perfusion to maintain its exceptionally high metabolic activity, even moderate disturbances of microvascular circulation rapidly compromise cellular survival.

One of the principal findings of this investigation was the presence of endothelial dysfunction. Swelling of endothelial cells, narrowing of capillary lumens, and decreased expression of endothelial nitric oxide synthase indicate impairment of normal vascular autoregulation. Nitric oxide is essential for maintaining adequate vascular relaxation and tissue perfusion. Reduced nitric oxide production increases vascular resistance, diminishes blood flow, and further aggravates ischemia. Consequently, endothelial dysfunction represents both an initiating factor and a perpetuating mechanism in optic nerve ischemia.

Persistent tissue hypoxia activated hypoxia-inducible factor-1 alpha, reflecting adaptive cellular responses aimed at restoring oxygen homeostasis. Increased vascular endothelial growth factor expression suggested an attempt to stimulate angiogenesis; however, this compensatory response was insufficient to restore normal microvascular circulation during the acute phase of injury. These observations indicate that endogenous vascular repair mechanisms cannot adequately compensate for extensive ischemic damage.

The inflammatory response observed in this study also contributed substantially to disease progression. Activation of astrocytes and microglia promoted production of inflammatory cytokines, reactive oxygen species, and proteolytic enzymes that intensified secondary neuronal injury. Although inflammatory cells participate in removal of damaged tissue, prolonged activation creates a toxic microenvironment that accelerates retinal ganglion cell apoptosis and optic nerve degeneration.

Mitochondrial damage represented another critical pathological feature linking microvascular insufficiency with neuronal death. Reduced oxygen availability impaired oxidative phosphorylation, decreased ATP production, and increased oxidative stress. Energy depletion disrupted ionic homeostasis and initiated apoptotic signaling pathways responsible for progressive retinal ganglion cell loss. Preservation of mitochondrial function may therefore represent an important therapeutic strategy for limiting ischemic injury.

The close relationship observed between capillary degeneration and axonal loss emphasizes that preservation of microvascular integrity is essential for maintaining optic nerve function. Therapeutic interventions directed toward improving endothelial function, enhancing microvascular perfusion, reducing oxidative stress, inhibiting inflammatory responses, and protecting mitochondria may significantly decrease the severity of ischemic optic neuropathy. Early identification of microcirculatory dysfunction using advanced vascular imaging techniques may also facilitate timely therapeutic intervention before irreversible neuronal degeneration occurs.

5. Conclusion

Microcirculatory disorders play a central role in the pathogenesis of acute ischemic optic neuropathy by initiating and sustaining optic nerve ischemia through endothelial dysfunction, capillary narrowing, impaired vascular autoregulation, and reduced tissue perfusion. These vascular abnormalities trigger a complex cascade of pathological processes including hypoxia, oxidative stress, mitochondrial dysfunction, inflammation, apoptosis, demyelination, and progressive degeneration of retinal ganglion cells and optic nerve axons.

Comprehensive histopathological, immunohistochemical, morphometric, and ultrastructural analyses demonstrate that the severity of neuronal injury is closely associated with the degree of microvascular impairment. These findings emphasize that preservation of microcirculatory function should be considered a primary therapeutic objective in the prevention and treatment of acute ischemic optic neuropathy. Future investigations should focus on the identification of early microvascular biomarkers, development of targeted endothelial-protective therapies, modulation of inflammatory pathways, enhancement of mitochondrial resilience, and stimulation of vascular regeneration to improve visual outcomes and reduce irreversible optic nerve damage.

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