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The Role of Neutrophils, Lymphocytes, and Platelets in Ischemic Stroke

İskemik İnmede Nötrofiller, Lenfositler ve Trombositlerin Rolleri

Hatice Ferhan Kömürcü

ABSTRACT

Pathological changes developing in acute ischemic stroke are associated with inflammation and immune events. In the process of cerebral ischemia, platelets, neutrophils, and lymphocytes have an important role in inflammatory and immune events. Uncertainties about the effects of blood cells along with immunity in sterile inflammatory response after stroke persist. Blood cells play an important role in the development of ischemic damage in acute stroke. Platelets contribute to the migration of neutrophils from the circulation to the ischemic area to open the path in the vascular wall and enter into the damaged area. Besides, lymphocytes are involved in the damage, sometimes positive and sometimes negative mechanisms in acute stroke. Dynamic changes of these cells may be related to the prognosis, determining the degree of neurological damage of stroke. Investigation of the effects of blood cells as mediators and pathophysiological mechanisms in stroke will contribute to the determination of treatment approaches and prediction of prognosis. This article reviews recent studies on the role of neutrophils, lymphocytes, and platelets in the development and the prognosis of ischemic damage in acute stroke.

Keywords: Ischemic stroke; Leukocyte; Lymphocyte; Neutrophil; Platelet; Stroke.

ÖZET

Akut iskemik inmede gelişen patolojik değişiklikler, inflamasyon ve immün olaylarla ilişkilidir. Serebral iskemi sürecinde trombositler, nötrofiller ve lenfositler, inflamatuvar ve immün olaylarda önemli bir role sahiptir. İnme sonrası steril inflamatuvar yanıtta kan hücrelerinin ve bağışıklığın etkilerine ilişkin belirsizlikler devam etmektedir. Akut inmede iskemik hasarın gelişmesinde kan hücreleri önemli bir rol oynar. Trombositler, damar duvarındaki yolu açmada dolaşımdan iskemik bölgeye nötrofillerin göçüne katkıda bulunur ve nötrofiller hasarlı bölgeye geçer. Ayrıca akut inmede, lenfositler hasara bazen pozitif bazen de negatif mekanizmalarla katılır. Bu hücrelerin dinamik değişiklikleri, inmenin nörolojik hasar derecesi ile ilişkili olabilir. İnmede kan hücrelerinin ve patofizyolojik mekanizmaların araştırılması tedavi yaklaşımlarının belirlenmesine ve prognozun öngörülmesine katkı sağlayacaktır. Bu makale, akut inmede iskemik hasarın gelişimi ve prognozunda nötrofillerin, lenfositlerin ve trombositlerin rolüne ilişkin son çalışmaları gözden geçirmektedir.

Anahtar sözcükler: İnme; iskemik inme; trombosit; lökosit; lenfosit; nötrofil.

Stroke is the second cause of death worldwide and the third cause of disability. Ischemic strokes make up approximately 70% of acute strokes.[1] The underlying pathophysiological mechanisms in ischemic stroke are still not fully understood. Thrombotic events and inflammation (thromboinflammation) are very important factors in cerebral ischemia.[2,3] Inflammatory response plays a key role in the development of brain injury after acute ischemic stroke.[2] Obstruction or severe stenosis of the cerebral artery causes necrotic death of the brain tissue (infarction). After the onset of cerebrovascular disease, the ischemic cell death pattern is mainly necro-

Department of Neurology, University of Health Sciences, Fatih Sultan Mehmet Training and Research Hospital, Istanbul, Türkiye

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Correspondence:
Dr. Hatice Ferhan Kömürcü. Sağlık Bilimleri Üniversitesi, Fatih Sultan Mehmet Eğitim ve Araştırma Hastanesi, Nöroloji Kliniği, Istanbul, Türkiye
Phone:
+90 532 594 47 02
e-mail:
ferhankomurcu@yahoo.com

sis and inflammation develops around dead brain cells. Cellular components released from dying brain cells are recognized by immune cells in the infarction zone, which, then, activate immune cells to produce various inflammatory cytokines and chemokines. Therapeutic goals for ischemic stroke can be determined by clarifying in detail cellular and molecular mechanisms of ischemic inflammation caused by natural or acquired immunity.[4,5]

Factors such as the formation of tissue damage with ischemic stroke, the release of various proteolytic enzymes, the appearance of reactive oxygen species (ROS) and inflammatory mediators, development of tissue reperfusion damage caused by early thrombolytic therapy or thrombectomy, and changes in the number of leukocytes and platelets may be related to the early and long-term course and prognosis of the disease. Platelets and neutrophils play an important role in inflammatory events that develop in atherosclerosis, thrombosis, and acute ischemic stroke.[4]

The inflammatory reaction following acute cerebral ischemia increases the infarct area and neurological deficit. Brain cells in the ischemic area rapidly synthesize protein and cytokines associated with cellular communication, and cytokines become important mediators of the endothelium-leukocyte relationship by causing hematogenous inflammatory cell flow in the ischemic area of the brain. In systemic inflammation, neutrophils are specialized cells of the immune system that responds first. Platelets are important for the development of thrombosis and the transition of neutrophils into tissue at the inflammatory stages. In the inflammatory process initiated by neutrophils, lymphocytes give an adaptive response.[6] Neutrophils act to increase tissue damage through the release of inflammatory mediators, ROS, and various proteolytic enzymes.[6]

Neutrophils and Platelets in Ischemic Stroke

Neutrophils are essential components of the immune response in congenital immunity. They provide defense against infection and also work in non-microbial injury sites.[7] Neutrophils in the circulation enter into the injured cerebral area shortly after ischemia, contributing to the disruption of the blood–brain barrier and tissue damage through different mechanisms.[6] Neutrophils are important sources of matrix metalloproteinase-9 (MMP-9), which can open the blood–brain barrier from the lumen of the blood vessel by effecting tight junction protein directly, absorb endothelial cells, and affect the basement membrane.[8] Neutrophil-derived metalloproteinases are released from neutrophils after stroke, along with some other factors.[6] ROS, myeloperoxidase, elastase, cathepsin G, proteinase-3, cytokines, and chemokines can disrupt the neurovascular unit, which increase blood–brain barrier permeability and hemorrhagic transformation.[9]

Platelets are blood cells involving in a large number of physiological functions. They circulate in the blood vessels without being activated under normal physiological conditions and without interacting with the vascular endothelium.[10] The role of platelets in hemostatic functions includes their adhesion to and accumulation in the damaged vascular structure.[11] Platelets protect the vascular structure against leakage, and they are considered to be the main actors of many pathophysiological processes, such as ensuring vascular integrity of developing vessels and lymphatics under inflammatory condition.[12] Platelets first form a platelet thrombosis and cluster adjacent to the place of vascular damage. Coagulation is supported by increasing thrombin production. These two conditions play a key role in classical hemostasis.[13] Platelets are the initiators and regulators of inflammation in the vascular wall with their secreted mediators such as adenosine diphosphate, thromboxane, and von Willebrand factor.[14] When they are stimulated, they release inflammatory molecules and adhesion molecules, and activation of leukocytes and platelets, together with inflammatory cells, which promote vascular inflammation, leading to atherosclerosis.[15] Functions of platelets may be abnormal in areas with impaired blood flow, such as atherosclerotic plaque rupture or abnormal stenosis.[16] Overactivation and aggregation of platelets can cause thrombosis and lead to vascular occlusion, and cardiovascular and cerebrovascular events may develop.[15] In acute ischemic stroke, circulating platelet distribution width and mean platelet volume increase.[17,18] Platelets can be depleted due to thrombosis which may result in decreased platelet production.[17]

Platelets act as triggers for neutrophil extravasation into inflammatory sites, but the mechanisms and tissue-specific aspects of these interactions are not fully understood.[7] Neutrophil infiltration into the brain is platelet dependent and is associated with GPIb α, the platelet membrane glycoprotein GPIb has an important function in thrombotic processes,[7] because it is necessary for the platelets to adhere to the vessel wall first.[3] Furthermore, GPIb has a binding region for Mac-1. Integrin Mac-1expressed from neutrophils and monocytes has been shown to play a role in adhesion

of leukocytes to platelets, and leukocyte-platelet complexes may increase inflammation.[19] A potential mechanical link is reported between GPIb/Mac-1 interactions and thrombosis and inflammation.[20] Platelet GPIb is one of the potential molecular targets in inflammation and thrombosis.[3] GPIb α blockade in brain inflammation causes a significant decrease (44%) in platelet-induced neutrophil invasion while maintaining circulating platelet counts. The blockade of platelet GPIb α may limit the harmful effects of excessive inflammation while minimizing hemorrhagic complications of platelet reduction in the brain.[7,3] While the natural immune response provides rapid defense against infection, injury or disease, and prolonged or excessive neutrophil-induced inflammation damages adjacent healthy tissue and is particularly harmful during central nervous system inflammations, where repair capacity is limited.[21]

Interaction of platelets with neutrophils before going out of the vein is necessary to trigger the binding and rolling of neutrophils onto inflamed venules.[7] Platelet P-selectin is released from activated platelets. Neutrophils contain granules that bind P-selectin glycoprotein ligand-1.[7] These findings suggest that platelets are required for extravasation of neutrophils into inflammatory sites which depend on the specific tissue location. It has been shown that platelets are necessary for neutrophil infiltration into the peritoneum, skin, and brain, but not for the lung, where compensatory mechanisms provide greater flexibility when dealing with the pathogen. In addition, brain platelet-mediated neutrophil invasion is dependent on receptor GPIb. These molecules can be targeted to reduce the risk of bleeding in the brain and limit excessive inflammation.[7] Thrombus formation and inflammation are closely related to acute ischemic stroke. Blocking platelet GPIb can improve thromboinflammation.[3]

Neutrophils infiltrate the ischemic region with cytokines and chemokines that are released in the ischemic area hours after ischemic stroke.[22] The blood–brain barrier is damaged by MMP9 release.[23] Proteases, free oxygen radicals, and other inflammatory mediators lead to brain edema and brain damage.[24]

In atherosclerosis, neutrophils cause endothelial dysfunction and lead to vascular inflammation by secretion of oxidoreductases, biologically active small molecules, extracellular proteases, and antimicrobial peptides.[20] Platelets and neutrophils, which affect the progression of the disease from the platelet neutrophil aggregates, support plaque rupture, trigger thrombosis and embolism, and cause inflammation and thrombosis.[25] In acute ischemic stroke, platelets are over-consumed due to thrombosis, while platelet counts decrease, and the number of neutrophils increases due to inflammation.[22] Our study supports these findings and shows that there is a decrease in platelet and increase in neutrophil counts in acute and subacute periods of ischemic stroke after rtPA and thrombectomy treatments.[26]

When neutrophils are stimulated with pathogens, some biochemical agents (phorbol-12-myristate-13-acetate, lipopolysaccharide, IL-8, TNF-α, monosodium urate crystals, nitric oxide), autoantibodies, and molecules such as immune complexes form structures defined as “neutrophil extracellular traps” (NETs).[27,28] Nucleus content is released out of the cell as a result of a series of intracellular reactions that occur in neutrophils activated by encountering pathogens or certain molecules. Since some cells other than neutrophils also form this structure, this structure is called “ETosis.”[29] NETosis is a cell death process in many ways different from necrosis and apoptosis. Neutrophils develop NETs in a few minutes in the presence of platelets and the lipopolysaccharide component of pathogens.[30] NETosis, which is an important element of natural immunity, causes unfavorable conditions in the organism if it is formed at the wrong time or in a low-density and undesired place.[27] Neutrophil-platelet interaction triggers the release of NETs during sepsis. Circulating NETs can damage vessel endothelium. At the same time, these chromatin strands form scaffolds in the circulation, allowing the thrombus to be shaped, thus causing blood flow disturbance. This phenomenon indicates that NETosis increases the risk of thrombosis.[27] Mechanisms related to factors released from neutrophils can cause ischemic brain damage. Extracellular chromatin and histones increase cerebral ischemia-reperfusion injury in mice.[31] NETs disrupt the blood–brain barrier and play a role in tissue damage.

Lymphocytes in Ischemic Stroke

The brain contains a lymphatic structure formed by combining the “glymphatic” system, lymphatic system, and glial cells.[13] The immune response of antigen-specific T-cells is assumed to be elicited by some of its antigens, which is produced from damaged brain tissue and transferred from the brain into the cervical lymph nodes.[32]

T- and B-cells are major actors in acquired immunity and are found mainly in the blood, spleen and lymph nodes. After

ischemic stroke, the number of peripheral T- and B-cells decreases, significant atrophy is seen in the spleen and lymph nodes.[4] This is thought to be due to the hyperstability of the sympathetic nerve after ischemic stroke, which induces apoptosis of T- and B-cells in the lymphatic organs. As a result, there is a temporary immune system suppression that is common in patients with ischemic stroke with pneumonia. The dynamics of lymphocytes in the periphery may be associated with complications of post-ischemic stroke infection.[33]

Brain ischemia quickly activates the cerebral microvascular structure. Endothelial adhesion molecules increase in number.[3] Subendothelial matrix proteins are exposed to the bloodstream in damaged vessels, thereby providing a medium for T-cell-endothelium, platelet-endothelium, and T-cell-platelet contact. T-cells cause microvascular dysfunction and further increase thrombosis formation in the early stage after vascular occlusion.[3,20] Targeting platelets by blocking the early adhesion of platelets to the vessel walls also reduce inflammatory processes associated with T-cells after a stroke.[3]

Approximately 40% of infiltrated T-cells in the ischemic brain are CD4-positive helper T-cells, while 30% of them are CD8-positive cytotoxic T-cells. Antigen-specific immune responses play an important role in ischemic brain injury.[34] There are several subsets of helper T-cells detected in the infected area, among which interferon gamma (IFN-γ) producing and regulatory T-cells (Treg) play a role in immune tolerance. The function of IFN-γ and Treg in ischemic stroke is complex, because these subgroups have been reported to be neuroprotective or sometimes neurotoxic.[35]

Infiltration of T-cells into the ischemic brain is induced by the activation of vascular endothelial cells. Increased expression of vascular cell adhesion molecule-1 in endothelial cells is important for T-cell infiltration that interacts with a4β1 integrin (VLA-4) in T-cells. Compared to macrophages and neutrophils, the infiltration of T-cells is observed in a relatively delayed phase (24 h after onset of stroke).[36] If a therapeutic agent targeting T-cells can be developed, there may be an opportunity to expand the therapeutic time window.

Antigen-specific T-cells (αβT cells) make up about 70% of T cells in the ischemic brain, while T-cells that elicit antigen-independent innate immune response make up about 20% of infiltrated T-cells. Since some self-antigens (such as β2 microglobulin) have been identified for activation of T-cells, it is possible to activate γδT cells with self-antigens in advance. γδT cells trigger rapid inflammation compared to αβT cells. γδT cells are stimulated with IL-23 activated myeloid cells.[37] IL-17, one of the most important inflammatory cytokines for neuroinflammation, enhances the inflammatory effect of neutrophils and activates vascular endothelial cells to increase the infiltration of immune cells by destroying the blood–brain barrier.[4] In mice lacking IL-23 or IL-17, the infarction volume can be reduced by continuously preventing inflammation in the subacute phase of ischemic brain injury. Inflammation caused by T-cells is closely related to the pathology of brain infarction. Therefore, targeting T-cells are a promising strategy for the development of therapeutic agents that can expand the therapeutic time window for the treatment of ischemic stroke.[4]

Lymphocyte counts may reflect the effect of acute physiological stress, and relative lymphopenia may reflect cortisol-related stress response and sympathetic tone, as well as increase the production of pro-inflammatory cytokines that aggravate ischemic damage.[38,39] Low lymphocyte count should not only be evaluated as an initial response to serious stroke in patients with hemorrhagic transformation. This phenomenon may also be an indication of activation involving protective mechanisms in the ischemic brain. In experimental findings, regulator T-cells, which are the subtypes of lymphocytes, play a key role in correcting the inflammatory response and assume important tasks as an immunomodulator protecting the brain in acute stroke.[40]

However, pro-inflammatory lymphocytes, other subtypes of lymphocytes, may have a disruptive effect in ischemia reperfusion injury.[41] It is not certain, in which lymphocyte subtype has a dominant role in the pathophysiology of cerebral ischemia, and lymphocyte depletion has been shown to have a negative effect in hemorrhagic transformations.[41]

The Relationship Between Neutrophil, Lymphocyte, and Platelet Ratios With Prognosis of Stroke

The ratio of neutrophil and lymphocyte counts (NLR) reflects the balance between neutrophils and lymphocytes, showing the immunological condition in detail. NLR is superior to only neutrophil count or lymphocyte count to make a differential diagnosis of hemorrhagic transformation. Inflammatory cytokines released by neutrophils can trigger lymphocyte apoptosis.[38] Stroke, infections, and early hospital infections can increase leukocytes in stroke and signal poor

prognosis.[42] In predicting the progression and severity of the disease in patients with acute cerebral infarction, lymphocyte count can be compared with the NLR and platelet/lymphocyte ratio (PLR).[38] It has been reported that PLR can also be used as an inflammatory marker that can reflect the systemic inflammatory response similar to NLR.[14] Some researchers have shown that PLR can be used as a marker for an increased inflammatory response due to the release of many mediators from platelets and that high PLR values in acute ischemic stroke are associated with poor prognosis and size of the infarction area.[14] It has been reported that NLR predicts short-term mortality risk in ischemic stroke, a complication of atherosclerotic processes.[43]

NLR has been shown as a determinant finding for short- and long-term results in patients with ischemic stroke.[38] In the previous studies, high NLR values have been shown to independently increase the risk of stroke in atrial fibrillation.[44] The high numbers of neutrophils are considered to be an indicator of an unfavorable condition since they may further aggravate tissue damage through the release of inflammatory mediators, ROS, and various proteolytic enzymes. For these reasons, patients with infections or other conditions such as cancer pose a greater risk for hemorrhagic transformation after IV rtPA treatment, as they already induce potential changes in NLR.[38] NLRs show significant temporary changes after ischemic stroke.[45] In our study, we reported a dynamic change in the counts and ratios of neutrophils, lymphocytes, and platelets in the early period of the ischemic stroke in patients who underwent thrombolytic therapy or thrombectomy.[26]

In predicting the progression and severity of the disease in patients with acute cerebral infarction, lymphocyte count can be compared with NLR and PLR. Compared with the good disease course group of acute cerebral infarction, the number of lymphocytes in the worse course group is significantly reduced.[46] As inflammatory and immune biomarkers, lymphocyte counts can determine the 30-day poor disease course and severity in acute cerebral ischemia, similar to the performance of NLR and PLR.[46]

The NLR reflects systemic inflammation and plays an important role in the treatment of ischemic stroke. NLR is a determinant in showing a 3-month functional course in symptomatic intracranial hemorrhages.[47] Decreased number of leukocytes before thrombolysis is associated with early neurological improvement in acute ischemic stroke patients.[48] NLR is an independent determinant that can be used to predict intracranial hemorrhage after endovascular thrombectomy in acute ischemic stroke.[49] Immune response and neurovascular interaction play a role in reperfusion injury and intracranial bleeding after stroke. NLR is higher in patients with a poor post-stroke disease course, and especially, NLR >5 has been reported as an independent risk factor. An increase in NLR is associated with hemorrhage after ischemic stroke and the risk of mortality within 3 months.[50]

Low platelet neutrophil ratio (PNR) also indicates poor prognosis.[50] PNR may be an independent prognostic factor in acute ischemic stroke. Platelet activation and aggregation are important in acute ischemic stroke. Increased activation and aggregation of platelets can lead to vascular occlusion and thrombosis in ischemic stroke and ischemic heart disease.[15]

Conclusion

It is known that pathological changes in acute ischemic stroke are associated with sterile inflammation, immune response, and dynamic changes in blood cells. Platelets, neutrophils, and lymphocytes play a major role in stroke. Platelets support the development of ischemia and contribute to inflammation by inducing thrombosis with different mechanisms involving coagulation factors and released proteases. Neutrophils are the cells that function priorly in the brain after a stroke and infiltrate the damaged area in the anoxic brain tissue. Lymphocytes also participate in this process by showing neuroprotective and sometimes neurotoxic effects. In addition, inflammatory mediators are released from the ischemic brain tissue area and aggravate brain injury. Examining the effects of blood cells on acute stroke, the mediating molecules, and the formed cascades will guide the development of treatment goals to prevent or reduce potential brain injury.

Disclosures

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