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THE ROLE OF COVID-19 IN THE DEVELOPMENT OF ISCHEMIC STROKE: PATHOGENETIC AND MOLECULAR MECHANISMS

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Abstract

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has evolved into a global health challenge affecting multiple organ systems. Although initially recognized as a respiratory disease, accumulating clinical and experimental evidence indicates that COVID-19 is a systemic disorder with significant vascular and neurological implications. One of the most severe neurological complications associated with COVID-19 is ischemic stroke. The mechanisms underlying COVID-19-

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associated stroke are multifactorial and involve endothelial dysfunction, hypercoagulability, systemic inflammation, hypoxia, and genetic susceptibility. This article reviews the pathogenetic and molecular mechanisms linking SARS-CoV-2 infection with the development of ischemic stroke, emphasizing the roles of endothelial injury, cytokine-mediated inflammation, hypoxia-inducible factors, and vascular endothelial growth factor (VEGF). Understanding these mechanisms is crucial for the development of effective preventive and therapeutic strategies aimed at reducing cerebrovascular complications in patients with COVID-19.

Keywords: Ischemic stroke, MTHFR, MTRR, MTR, VEGFA, Hyperhomocysteinemia, Endothelial dysfunction, HIF-1

Introduction

COVID-19 BILAN KASALLANGAN ISHEMIK INSULT BEMORLARDAGI TROMBOFILIYA GENLARINING XUSUSIYATLARI

Annotatsiya

COVID-19 infeksiyasining jiddiy asoratlaridan biri ishemik insult hisoblanadi, uning chastotasi nafaqat kasallikning o'tkir bosqichida, balki infektsiyadan tuzalgan shaxslarda ham sezilarli darajada ortib borayotgani kuzatilmoqda. Post-COVID sindromiga chalingan bemorlarda prokoagulyant va antikoagulyant tizimlar o'rtasidagi muvozanatning buzilishi sababli tromboz rivojlanishi xavfi yuqori darajada saqlanib qolmoqda. Ushbu holatning asosiy sabablaridan biri folat kislotasi metabolizmi genlari (MTHFR, MTRR, MTR) va angiogenez faktori – VEGFA bilan bog'liq bo'lishi taxmin qilinadi. Folat sikli genlarining yetarli darajada ifodalanmasligi (ekspressiya qilinmasligi) yoki ulardagi kamchiliklar surunkali endotelial disfunktsiyaga olib keladi, bu holat COVID-19 infektsiyasi fonida yanada og'irlashadi. Shu bilan birga, VEGFA omilining past ekspressiyasi ishemik hududlarda yangi qon tomirlari hosil bo'lishi (angiogenez) jarayonini buzishi orqali ishemik insult xavfini oshiradi. O'zbekiston populyatsiyasida ushbu muammolarga olib keluvchi polimorf genlarni tadqiq

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qilish, aholi orasida ushbu asoratga moyil shaxslarni aniqlashga yordam beradi. Bu esa, o'z navbatida, ushbu shaxslarda maxsus profilaktika va davolash chora-tadbirlarini qo'llash orqali ishemik insult va COVID-19 ning boshqa jiddiy asoratlaridan himoya qilish uchun muhim ma'lumot manbai bo'lib xizmat qiladi.

Kalit so'zlar: Ishemik insult, MTHFR, MTRR, MTR, VEGFA, gipergomosisteinemiya, endotelial disfunktsiya, HIF-1.

Особенности Генов Тромбофилии у Пациентов с Ишемическим Инсультом, Ассоциированным с COVID-19

Аннотация

Ишемический инсульт является одним из наиболее тяжелых осложнений, ассоциированных с инфекцией COVID-19, частота возникновения которого заметно возрастает не только в острой фазе заболевания, но и у лиц, перенесших данное инфекционное поражение. У пациентов, страдающих постковидным синдромом, сохраняется существенно повышенный риск тромбообразования, что обусловлено дисбалансом между прокоагулянтными и антикоагулянтными системами. Предполагается, что одной из ключевых причин развития этого патологического состояния является его взаимосвязь с генетическими полиморфизмами генов фолатного цикла (MTHFR, MTRR, MTR) и фактора ангиогенеза – VEGFA. Недостаточная экспрессия или функциональные нарушения генов фолатного цикла могут приводить к формированию хронической эндотелиальной дисфункции, состояние которой усугубляется на фоне COVID-19. Параллельно, снижение экспрессии фактора VEGFA нарушает процесс формирования новых кровеносных сосудов (ангиогенеза) в ишемических зонах, тем самым повышая предрасположенность к ишемическому инсульту. Исследование данных полиморфных генов, способствующих возникновению упомянутых проблем в узбекской популяции, окажет содействие в идентификации лиц, предрасположенных к развитию данного осложнения. Полученные результаты, в свою очередь, станут ценным источником информации для разработки персонализированных стратегий профилактики и лечения, направленных на

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защиту этих лиц от ишемического инсульта и иных тяжелых последствий COVID-19.

Ключевые слова: Ишемический инсульт, MTHFR, MTRR, MTR, VEGFA, Гипергомоцистеинемия, Эндотелиальная дисфункция, HIF-1.

Since its emergence in late 2019, COVID-19 has spread rapidly across the globe and has been diagnosed in hundreds of millions of individuals. The causative agent, SARS-CoV-2, belongs to the coronavirus family and represents the third major coronavirus outbreak in the 21st century after SARS-CoV and MERS-CoV. Compared with previously known coronaviruses, SARS-CoV-2 demonstrates remarkably high transmissibility and adaptive capacity, enabling the rapid emergence of new viral variants. A key feature of the virus is its ability to infect a wide range of host cells via the angiotensin-converting enzyme 2 (ACE2) receptor. These receptors are widely expressed in multiple tissues, including alveolar epithelial cells, enterocytes of the gastrointestinal tract, neurons, cardiomyocytes, cholangiocytes of the liver, renal proximal tubular cells, and cells of the urogenital tract. Severe forms of COVID-19 are characterized by atypical pneumonia, acute respiratory distress syndrome (ARDS), pulmonary fibrosis, systemic inflammatory response syndrome, autoimmune reactions resembling vasculitis, and a high incidence of thrombotic and thromboembolic complications. Importantly, these complications may involve the central nervous system (CNS), resulting in conditions such as ischemic stroke and myocardial infarction. Over the course of the pandemic, it has become evident that COVID-19 is associated with a wide range of neurological manifestations. These include cerebrovascular diseases, encephalitis, peripheral neuropathies, neuromuscular disorders, cognitive impairment, psychiatric disturbances, and long-term neuropsychological complications. Among these manifestations, ischemic stroke represents one of the most severe and potentially life-threatening complications.

Neurological Manifestations of COVID-19.

Patients recovering from COVID-19 frequently develop neurological and psychiatric symptoms. Clinical studies report the occurrence of various complications, including ischemic stroke, peripheral neuropathy, myopathy, Bickerstaff encephalitis, Guillain–Barré syndrome, neuralgia, and myasthenic

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syndromes. Psychiatric and neuropsychological complications are also common. Post-COVID depression has been reported in approximately 28–39% of patients, while anxiety disorders occur in nearly 35%. Other neurological manifestations include anosmia, ageusia, psychosis, suicidal ideation, cognitive impairment, post-traumatic stress disorder, delirium, and sleep disturbances. These neurological complications arise from several pathogenetic mechanisms triggered by SARS-CoV-2 infection.

Pathogenetic Mechanisms Linking COVID-19 and Ischemic Stroke

Hypoxic-Ischemic Mechanism. Severe pulmonary involvement in COVID-19 leads to impaired gas exchange and systemic hypoxia. Persistent oxygen deficiency disrupts normal metabolic processes and contributes to endothelial dysfunction. Hypoxia also promotes coagulation abnormalities by activating procoagulant pathways and suppressing fibrinolysis. Elevated levels of fibrinogen and D-dimer, combined with thrombocytopenia resulting from platelet consumption, serve as important biomarkers indicating an increased risk of thrombotic events, including ischemic stroke. In this context, cerebral ischemia may occur due to thrombotic occlusion of cerebral vessels or as a consequence of systemic hypoxic injury to neural tissue.

Neuroinvasive Mechanism. SARS-CoV-2 has demonstrated the ability to invade the central nervous system through multiple routes. One of the most probable pathways involves retrograde axonal transport through the olfactory nerve, allowing the virus to reach the brain from the nasal cavity. Another potential route involves the vagus nerve, which innervates the respiratory and gastrointestinal systems. In addition, viral RNA has been detected in the cerebrospinal fluid of certain COVID-19 patients, suggesting direct viral involvement in the CNS. Gastrointestinal involvement may further contribute to neurological complications. Damage to the intestinal barrier can result in endotoxemia, allowing bacterial endotoxins to enter systemic circulation. These endotoxins may influence CNS function both directly and indirectly by stimulating excessive cytokine production.

Hypothalamic Mechanism. During the viremic phase of infection, SARS-CoV-2 may affect the hypothalamus. This region of the brain is particularly vulnerable because the blood-brain barrier is relatively weaker in hypothalamic structures.

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Moreover, both neurons and glial cells within the hypothalamus express ACE2 receptors, making them susceptible to viral entry. Hypothalamic dysfunction can disrupt autonomic regulation, endocrine balance, and inflammatory responses, potentially contributing to cerebrovascular complications.

Cytokine-Mediated Mechanism. A hallmark of severe COVID-19 is the excessive activation of the immune system, often referred to as a "cytokine storm." SARS-CoV-2 activates Toll-like receptors (TLRs), triggering intracellular signaling pathways that lead to the massive release of pro-inflammatory cytokines. These cytokines include interleukin-6, interleukin-1β, tumor necrosis factor-α, and other inflammatory mediators. The resulting systemic inflammation damages endothelial cells, increases vascular permeability, and promotes thrombogenesis. This cytokine-driven inflammatory environment plays a central role in the development of COVID-19-associated coagulopathy and cerebrovascular complications.

Endothelial Dysfunction in COVID-19. Recent research suggests that COVID-19 should be considered not only a respiratory infection but also a vascular disease characterized by widespread endothelial injury. Under normal physiological conditions, endothelial cells maintain vascular homeostasis by performing several critical functions:

1. Regulation of vascular permeability
2. Control of vascular tone
3. Participation in hemostasis
4. Modulation of immune and inflammatory responses
5. Regulation of cellular proliferation
6. Control of cholesterol metabolism via oxidation of low-density lipoproteins

SARS-CoV-2 infection disrupts these functions by directly infecting endothelial cells through ACE2 receptors. This results in endothelial inflammation (endotheliitis), impaired nitric oxide production, and increased expression of procoagulant molecules.

Consequently, the balance between anticoagulant and procoagulant mechanisms shifts toward thrombosis, creating favorable conditions for both microvascular and macrovascular clot formation.

VEGF-A and Hypoxia-Induced Molecular Pathways. Members of the vascular endothelial growth factor (VEGF) family, including VEGF-A, VEGF-B, and

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placental growth factor (PlGF), play essential roles in angiogenesis and vascular remodeling. VEGF-A possesses significant neuroprotective and trophic properties. During cerebral ischemia, VEGF-A expression increases markedly in response to hypoxic stress. This promotes angiogenesis and enhances neuronal survival in ischemic brain tissue. Hypoxia activates hypoxia-inducible factors (HIF-1 and HIF-2), which regulate the expression of more than seventy genes involved in cellular adaptation to oxygen deprivation. Among these genes is VEGF, which stimulates new blood vessel formation. However, HIF activation also has prothrombotic effects. It enhances the expression of tissue factor and inhibits fibrinolysis, thereby increasing the risk of thrombosis. Genetic polymorphisms affecting the VEGF-A gene may impair angiogenic responses in certain individuals. In such cases, insufficient angiogenesis prolongs tissue hypoxia and exacerbates ischemic injury.

Discussion

The available scientific evidence indicates that COVID-19 is a complex systemic disease with profound effects on the vascular and nervous systems. The risk of ischemic stroke in patients with COVID-19 is significantly increased due to a combination of interconnected mechanisms. Unlike typical respiratory viral infections, SARS-CoV-2 exhibits a pronounced tropism for endothelial cells. Viral invasion of the vascular endothelium leads to widespread endothelial dysfunction and a prothrombotic state. The interaction between hypoxia, inflammation, and coagulation represents a key pathogenic pathway. Severe lung injury leads to systemic hypoxia, which activates HIF-dependent molecular pathways. While these pathways attempt to restore oxygen delivery through angiogenesis, they simultaneously enhance coagulation processes. Genetic factors further influence the severity of these responses. Variations in the VEGF-A gene may limit the effectiveness of angiogenic compensation, leading to persistent hypoxia and increased susceptibility to ischemic injury. Comorbid conditions such as hypertension, diabetes mellitus, obesity, and hyperhomocysteinemia also play a significant role. These disorders are associated with chronic endothelial dysfunction, which predisposes patients to thrombotic complications. Additionally, disturbances in the folate metabolic pathway involving enzymes such as MTHFR, MTR, and MTRR may elevate

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homocysteine levels. Hyperhomocysteinemia exerts cytotoxic effects on endothelial cells, reduces nitric oxide bioavailability, and enhances activation of the coagulation cascade. Thus, ischemic stroke in COVID-19 should be viewed not as an isolated complication but as the outcome of a complex interaction between viral infection, inflammation, endothelial injury, hypoxia, genetic predisposition, and metabolic disturbances.

Conclusion

COVID-19 is associated with profound systemic inflammation and endothelial dysfunction, which collectively contribute to the development of hypercoagulability and thrombotic complications.

The cytokine storm, hypoxia, and direct viral effects on endothelial cells significantly increase the risk of ischemic stroke. Patients with pre-existing conditions such as diabetes mellitus, arterial hypertension, obesity, and hyperhomocysteinemia are particularly vulnerable to severe cerebrovascular complications.

Furthermore, deficiencies in B-group vitamins and genetic polymorphisms affecting folate metabolism (MTHFR, MTR, MTRR) as well as VEGF-A may predispose individuals to more severe disease outcomes.

Identification of these risk factors through molecular and genetic screening may enable earlier intervention and personalized therapeutic strategies aimed at preventing cerebrovascular complications in patients with COVID-19.

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