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PATHOGENETIC ASPECTS OF IMPAIRED BLOOD RHEOLOGICAL PROPERTIES IN THE BRAIN AND NERVOUS SYSTEM IN BLUNT CLOSED HEAD TRAUMA

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Introduction and Relevance of the Problem

In the fields of modern neurosurgery, hematology, hemorheology, and intensive care, blunt closed head trauma (traumatic brain injury — TBI) remains one of the most severe and pressing clinical challenges [69, 96]. According to the latest statistical data from the World Health Organization, millions of people worldwide sustain TBI each year, making it one of the leading causes of death and long-term disability [69, 96]. In the Republic of Uzbekistan, the incidence of TBI continues to rise steadily due to road traffic accidents, occupational injuries, domestic incidents, and sports trauma, resulting in severe clinical complications in a significant portion of the population — including disturbances of blood rheological properties in the brain and nervous system [96, 69]. These disturbances represent one of the key pathogenetic mechanisms of secondary brain injury, leading to microcirculatory failure, cerebral ischemia, thrombosis, and hemorrhagic progression [8, 122].

Impairment of blood rheology in the acute phase of TBI reflects a bidirectional process. On one hand, endothelial injury and the release of tissue factor and brain microparticles from damaged neural tissue trigger hypercoagulation and microthrombosis [56, 114]. On the other hand, the influence of catecholamines, histone H4, and neutrophil extracellular traps (NETs) leads to platelet dysfunction and disruption of the microrheological properties of erythrocytes [61, 75]. These changes sharply reduce cerebral perfusion, amplifying hypoxia, oxidative stress, and inflammatory cascades [8, 122]. As a result, patients experience delayed neurological complications — cognitive impairment, epilepsy, decline in motor function, and even death [96, 69].

Numerous studies in hemorheology have demonstrated that reduced erythrocyte deformability, increased aggregation, and changes in osmotic resistance impair blood flow [3, 5]. For example, investigations using atomic force microscopy (AFM) and flow microchamber technology have clearly shown that in TBI, erythrocyte surface stiffening and reduced capillary permeability occur [4, 7, 23]. These mechanisms produce both local and systemic changes in the brain and nervous system [8, 40]. Endothelial dysfunction and NETs enhance erythrocyte adhesion to the endothelium, promoting microthrombus formation [56, 116]. Simultaneously, platelet dysfunction (loss of GPVI and GPIbα receptors) stimulates hemorrhagic progression and disrupts the balance of blood coagulation [61, 122].

The disruption of blood rheology in TBI pathogenesis plays an important role not only in the acute phase but also in long-term complications [96, 69]. Viscoelastic tests (TEG/ROTEM) and modern microrheological methods directly link changes in the biomechanical properties of erythrocytes to stasis and ischemia in cerebral microcirculation [23, 40]. In the context of Uzbekistan, this problem is particularly relevant: given the high rate of traumatism and the limited availability of modern laboratory diagnostics, early detection and correction of blood rheological disturbances could substantially improve clinical outcomes [96, 118]. Today, leading research centers worldwide are actively studying the molecular and cellular mechanisms of blood rheology in TBI [69, 70].

Meta-analyses conducted by Maegele and colleagues confirmed the association between coagulopathy and hemorheological disturbances and hemorrhagic progression [69, 70]. Vulliamy et al. elaborated on the mechanism of platelet "exhaustion" (through the action of histone H4 and catecholamines) [120, 122]. These studies demonstrate the critical importance of blood rheological disturbances not only for diagnosis but also for developing targeted therapeutic strategies [8, 61]. The significance of this topic lies in the fact that a thorough analysis of blood rheological changes in TBI — through laboratory markers, morphological assessment, and modern technologies — facilitates monitoring of patient status [55, 126].

This approach enables prevention of secondary injury and improvement of patient quality of life [96, 69]. In this regard, detailed investigation of the pathogenetic aspects of impaired blood rheological properties in the brain and nervous system in blunt closed head trauma represents one of the most promising directions in contemporary medical science [8, 122]. Application of research findings in clinical practice could improve patient prognosis and advance trauma and neurosurgery approaches within the Uzbekistan healthcare system [96, 69]. Disruption of blood rheology encompasses not only the coagulation system but also the microrheological properties of erythrocytes, plasma viscosity, and microcirculatory dynamics [3, 23]. These processes are closely interrelated, and a comprehensive analysis of each individually and in combination is essential [4, 7].

Epidemiological indicators of TBI show that severe forms of the disease frequently occur in young people and the working-age population, and rheological disturbances further worsen outcomes [69, 96]. Evidence from the scientific literature suggests that changes in blood rheological parameters in TBI may increase patient mortality risk by 2–3 times [96, 122]. Therefore, comprehensive study of this topic is of both theoretical and practical importance [8, 61]. Modern diagnostic methods — viscoelastic tests, AFM, and flow cytometry — enable early detection of rheological disturbances and support personalized treatment strategies [23, 55]. The theoretical and clinical data presented in this study will provide a foundation for deeper understanding of TBI pathogenesis and development of new therapeutic approaches [69, 96].

Pathophysiological Mechanisms and Topographic Classification

In blunt closed head trauma, impairment of blood rheological properties in the brain and nervous system proceeds through several complex pathogenetic mechanisms [69, 96]. First and foremost, endothelial dysfunction and the microvesicular mechanism play a primary role [56, 114]. When brain tissue is damaged, tissue factor and brain microparticles are released into the bloodstream, amplifying procoagulant activity [56, 114]. This process increases platelet

aggregation, promotes erythrocyte adhesion to the endothelium, and sharply raises blood viscosity [74, 132].

The second mechanism is platelet dysfunction [61, 122]. In TBI, elevated levels of catecholamines and histone H4 cleave the GPVI and GPIbα receptors on platelets via ADAM10 and ADAM17 enzymes [61, 122]. Consequently, ristocetin- and collagen-induced aggregation is reduced, producing a state of platelet "exhaustion" [75, 120]. This mechanism contributes to hemorrhagic progression and intensifies intracranial bleeding [10, 60].

The third mechanism is manifested in microrheological changes in erythrocytes [3, 23]. Erythrocyte deformability decreases, aggregation increases, and membrane rigidity rises [3, 23]. Studies using atomic force microscopy and flow microchamber technology have shown that in TBI the elastic modulus of erythrocytes increases, elevating resistance to capillary flow [4, 7]. Neutrophil extracellular traps (NETs) further amplify this process, promoting erythrocyte aggregation [56, 116].

The fourth mechanism is disruption of the fibrinolytic and coagulopathic cascade [15, 21]. Initially, excessive release of tPA leads to hyperfibrinolysis, followed by elevated PAI-1 causing hypofibrinolysis [15, 21]. This imbalance further complicates blood rheology and leads to microthrombosis or hemorrhage [59, 123].

Additionally, alterations in mitochondrial cardiolipin and erythrocyte osmotic resistance are of significant importance in the disruption of blood rheological properties [132, 50]. These mechanisms intensify local ischemia, thrombosis, and inflammation in the brain and nervous system, forming secondary injury [69, 96]. Research confirms that these changes independently increase the risk of death and disability [96, 122]. Pathophysiologically, the disturbances may be classified topographically as local (at the level of brain tissue) and systemic (in the circulatory system) [69, 96]. Local mechanisms directly disrupt microcirculation within the brain, while systemic mechanisms alter blood rheology throughout the entire body [8, 40]. Both mechanisms reinforce each other, giving rise to severe clinical conditions [56, 116].

The role of endothelial injury and NETs warrants special attention [56, 116]. NETs activate erythrocytes and platelets, producing thrombotic microangiopathy [56, 116]. Platelet dysfunction — through loss of GPVI and GPIbα — impairs aggregation and adhesion function [61, 122]. Microrheological disturbances of erythrocytes raise blood viscosity and lead to capillary stasis [3, 23]. Disruption of the fibrinolytic cascade produces an imbalance between clot formation and clot dissolution [15, 21]. Together, these mechanisms intensify hypoxia and necrosis in the brain and nervous system [69, 96]. Evidence from scientific studies indicates that these processes directly correlate with the severity of TBI, underscoring the necessity of early diagnosis and monitoring [55, 126].

A thorough understanding of the pathophysiological mechanisms provides the basis for correct application of laboratory and instrumental diagnostic methods [55, 99]. For example, viscoelastic tests and AFM allow real-time assessment of rheological changes [23, 40]. This approach enables dynamic patient monitoring and individualized therapy [96, 69].

Differential Analysis and Biochemical Characteristics of Key Rheological Markers

Detection of blood rheological disturbances in TBI is not limited to a single marker [55, 99]. This is a complex mosaic requiring integration of viscoelastic tests, morphological analyses, and

modern technologies [55, 126]. The first key marker is platelet function and aggregation [61, 122]. Using Multiplate or light transmission aggregometry, reduced responses to ristocetin and collagen are identified [61, 122]. Loss of the GPVI receptor is considered the most reliable indicator [61, 122].

The second marker is erythrocyte deformability and aggregation [3, 5]. AFM and flow microchamber methods demonstrate an increase in erythrocyte elastic modulus and elevated aggregation index [3, 23]. These changes directly reflect microcirculatory disturbances [4, 7].

The third marker is viscoelastic parameters (TEG/ROTEM) [55, 126]. Changes in R and K times and a decrease in maximum amplitude (MA) indicate coagulopathy and platelet dysfunction [55, 99]. The fourth marker is microparticles and NETs [56, 74]. Flow cytometry reveals elevated levels of brain microparticles and NETs, indicating systemic thrombosis risk [56, 114].

Table 1. Key rheological markers in TBI and their pathophysiological significance

Laboratory Marker	Change	Mechanism	Limitations
Platelet GPVI/GPIbα	Sharply decreased	ADAM10/17 activation	False results under catecholamine influence [61, 122]
Erythrocyte deformability	Decreased	Oxidative stress and membrane stiffening	May be masked by inflammatory background [3, 23]
Erythrocyte aggregation	Sharply increased	NETs and elevated fibrinogen	Similar in other thrombotic conditions [56, 116]
TEG/ROTEM MA	Decreased	Platelet dysfunction	Dependent on transfusion history [55, 126]
Microparticles (TF+)	Sharply increased	Brain tissue injury	Elevated in systemic inflammation [74, 114]

Table 2. Comparative analysis of hemorrhagic and thrombotic phenotypes

Marker	Hemorrhagic Phenotype	Thrombotic Phenotype	Characteristic in TBI
Platelet	Decreased	Increased	Dysfunction

aggregation			predominates [61, 122]
Erythrocyte aggregation	Moderate	Sharply increased	Strong NETs effect [56, 116]
Viscoelastic parameters	MA decreased	R and K shortened	Bidirectional disturbance [55, 126]

The correct combination and dynamics of these markers ensure a diagnostic conclusion [55, 99]. The limitations of each marker must be taken into account and integrated with the clinical context [30, 57].

Peripheral Blood Morphology and Modern Technologies

Morphological examination of a peripheral blood smear plays an important role in the visual assessment of blood rheological disturbances in TBI [23, 40]. Under light microscopy, erythrocyte shape, aggregates, and schistocytes are identified [23, 40]. Modern technologies — AFM, flow cytometry, and artificial intelligence-based analyzers — detect microrheological changes in erythrocytes with high precision [94, 23]. These methods capture subtle changes invisible to the human eye and predict early risk [23, 94].

Modern Therapeutic Approaches

Correction of blood rheological disturbances in the brain and nervous system in blunt closed head trauma (TBI) occupies a central place in modern therapeutic strategies [69, 96]. Tranexamic acid (TXA) is one of the most studied and effective hemostatic agents; it reduces hyperfibrinolysis and stabilizes blood rheology by inhibiting the fibrinolytic cascade [27, 28]. The CRASH-2 and CRASH-3 randomized clinical trials demonstrated that TXA significantly reduces mortality and blood transfusion volume in severe trauma and TBI [27, 28]. The mechanism of TXA involves suppression of tPA activity and restoration of PAI-1 balance, thereby correcting erythrocyte aggregation and platelet dysfunction [24, 97].

Plasma and platelet transfusion play an important role in correcting rheological disturbances [51, 6]. In patients with severe TBI receiving plasma and red blood cell transfusions at high ratios, mortality was significantly reduced [51, 10]. Platelet transfusion partially compensates for the loss of GPVI and GPIbα receptors and improves microcirculation [11, 60]. Desmopressin (DDAVP) restores ristocetin-induced aggregation by enhancing platelet activity and stimulating the release of von Willebrand factor [60, 81].

TEG/ROTEM-guided goal-directed therapy is considered the most effective approach in TBI [55, 126]. This method evaluates blood rheological parameters in real time and enables individualized therapy selection [55, 126]. Among innovative approaches, synthetic platelets (SynthoPlate™) and microparticle-clearing agents (lactadherin) occupy a special place [102, 134]. Synthetic platelets restore platelet aggregation and enhance hemostatic effect [102, 43]. Lactadherin reduces procoagulant activity by clearing microvesicles and improves survival in mouse models [134, 66].

Furthermore, recombinant factor VIIa and factor XIII supplementation are promising for stabilizing blood rheology [46, 112]. In clinical practice, combining TEG/ROTEM-guided care with TXA and plasma transfusion comprehensively corrects rheological disturbances in severe TBI [28, 55]. Experimental studies demonstrate the significant potential of synthetic platelets and microparticle-clearing agents in future clinical trials [102, 134]. Personalization of therapeutic strategies requires consideration of patient severity, transfusion history, and rheological parameters [55, 126].

Immune and Experimental Biomarkers

Immune and experimental biomarkers are of great importance for in-depth study of blood rheological disturbances in TBI and for developing new therapeutic approaches [56, 116]. The cytokine panel (IL-6, IL-8, and others) reflects the inflammatory cascade and NETs activity [56, 116]. NETs intensify erythrocyte aggregation, promote microthrombosis, and exacerbate neurological deficits [56, 116]. Flow cytometry-based monitoring of NETs and cytokine levels supports early identification of immune mechanisms underlying rheological disturbances [56, 120].

Experimental models (rat and pig) provide the foundation for clinical research on rheological changes [16, 88]. In rat models, platelet dysfunction and erythrocyte microrheological disturbances following TBI have been clearly demonstrated [88, 89]. In pig models, coagulopathy, endothelial damage, and inflammation following brain trauma and hemorrhage were studied in combination [103, 104]. These models clearly illustrated the procoagulant role of NETs and the role of microparticles [132, 133].

Mitochondrial cardiolipin and brain microparticles, as experimental biomarkers, disrupt blood rheology [132, 114]. In mouse models, these particles have been shown to trigger systemic coagulation [114, 132]. Agents such as lactadherin reduce rheological disturbances by clearing microvesicles [134, 135]. Among immune biomarkers, in addition to cytokines and NETs, free GPVI and histone H4 levels are also important [120, 122]. Using experimental models, new therapeutic agents — ADAM inhibitors and NETs blockers — are being developed [56, 116].

Variability of Markers and Limitations in Result Interpretation

Clinical context and dynamic monitoring are mandatory when interpreting marker results [30, 57]. Transfusion history is the greatest source of error, as platelet function and other parameters may yield false results following blood transfusion [12, 49]. Inflammation and chronic diseases (diabetes, atherosclerosis) mask markers [8, 73]. TEG/ROTEM results depend on the patient's transfusion history and may give falsely normal or reduced values [76, 99]. Immune and morphological markers (NETs, schistocytes) also have limitations [56, 23].

Chronic pathologies distort rheological markers [8, 50]. AFM and flow microchamber results may be subject to human error, although automated systems reduce this inaccuracy [23, 94]. Accounting for limitations, a multimarker panel (TEG/ROTEM + AFM + cytokines + NETs) achieves the highest accuracy [55, 56]. Dynamic monitoring enables real-time assessment of patient status [99, 126].

Conclusion

Impairment of blood rheological properties in the brain and nervous system in blunt closed head trauma remains one of the key pathogenetic mechanisms of secondary injury. These changes — encompassing decreased erythrocyte deformability, increased aggregation, platelet dysfunction,

and microvesicular activity — lead to cerebral ischemia and hemorrhagic progression. Laboratory markers, morphological analyses, and modern technologies play an important role in early diagnosis and monitoring. Modern therapeutic approaches (TXA, TEG/ROTEM-guided care, synthetic platelets) and immune-experimental biomarkers enable comprehensive correction of rheological disturbances. Future research will further elucidate these mechanisms, support the development of new therapeutic approaches, and improve traumatology outcomes within the Uzbekistan healthcare system.

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