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PLATELET DYSFUNCTION AS A PREDICTOR OF ISCHEMIC STROKES IN PATIENTS WITH CHRONIC BLOOD DISORDERS. LITERATURE REVIEW

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ABSTRACT

Introduction: Ischemic stroke remains a leading cause of global morbidity and mortality. Patients with chronic blood disorders exhibit a significantly elevated risk of ischemic stroke, attributable to complex hemostatic system impairments, with platelet dysfunction being a central component. Traditional cardiovascular risk factors do not fully account for the high incidence of cerebrovascular events in this population, underscoring the need to identify specific predictors linked to hematopoietic pathology.

Objective: The aim of this literature review is to systematize and analyze contemporary scientific data on the role of platelet dysfunction as a key predictor of ischemic strokes in patients with myeloproliferative neoplasms (MPNs), sickle cell anemia (SCA), and paroxysmal nocturnal hemoglobinuria (PNH).

Materials and Methods: A review of publications in peer-reviewed Russian and international journals available in the PubMed, Google Scholar, CyberLeninka, eLibrary, and other databases from 2000 to 2024 was conducted. Search keywords included: "platelets," "platelet dysfunction," "ischemic stroke," "myeloproliferative neoplasms," "sickle cell anemia," "paroxysmal nocturnal hemoglobinuria," "JAK2 V617F," "hypercoagulability."

Results: It was established that platelet dysfunction in chronic blood disorders is multifaceted. In MPNs, quantitative and qualitative anomalies are pivotal: thrombocytosis, heightened sensitivity to agonists, diminished response to antiplatelet therapy, and the presence of the somatic JAK2 V617F mutation, which is associated with a hypercoagulable phenotype. In SCA, the primary mechanisms involve chronic inflammation and platelet adhesion to activated endothelium and circulating erythrocytes. In PNH, a deficiency of complement regulatory proteins on the platelet membrane leads to their paradoxical hypersensitivity to complement activation. A comprehensive analysis of the data enabled the identification of key laboratory and molecular-genetic markers with prognostic value for stroke risk.

Conclusion: Platelet dysfunction is an integral component of the pathogenesis of ischemic strokes in patients with chronic blood disorders. Its assessment, which should extend beyond platelet count to include functional

activity (aggregation, activation marker expression, molecular-genetic profile), must be integrated into risk stratification algorithms. This approach paves the way for developing personalized strategies for the primary and secondary prevention of cerebrovascular events in this high-risk cohort.

KEY WORDS

Platelet dysfunction, ischemic stroke, chronic blood disorders, myeloproliferative neoplasms, polycythemia vera, essential thrombocythemia, sickle cell anemia, paroxysmal nocturnal hemoglobinuria, hypercoagulability, JAK2 V617F, thrombocytosis, platelet aggregation, predictor, cerebrovascular events.

INTRODUCTION

Ischemic stroke persists as a global medical and social challenge, ranking as the second leading cause of mortality worldwide and a primary cause of permanent disability in the adult population [Feigin et al., 2022, p. 12]. Despite significant progress in understanding its pathogenesis and developing therapeutic strategies, stroke incidence continues to rise, necessitating a deeper investigation into its etiology, particularly in specific high-risk groups.

This category includes patients with chronic blood disorders, among which myeloproliferative neoplasms (MPNs), sickle cell anemia (SCA), and paroxysmal nocturnal hemoglobinuria (PNH) hold a prominent place. The risk of ischemic stroke in these patients is dozens of times higher than in the general population [Marchioli et al., 2005, p. 85]. The pathogenesis of thrombotic complications in these conditions is complex and multifactorial, involving all components of the hemostatic system—the vascular wall, blood cells, and plasma coagulation factors. However, accumulating evidence indicates that the central element integrating these diverse pathological processes is the platelet.

Platelets, or thrombocytes, are traditionally viewed as the primary effectors of primary hemostasis. Yet, their role extends beyond the formation of a platelet plug. They are active participants in inflammation, immune response, angiogenesis, and vascular remodeling [Koupenova et al., 2018, p. 178]. In chronic blood disorders, platelets undergo profound alterations—both quantitative (thrombocytosis in MPNs, thrombocytopenia in PNH) and, more importantly, qualitative. Qualitative dysfunction, characterized by altered reactivity, metabolism, receptor apparatus, and secretory activity, transforms platelets from protective elements into agents of systemic prothrombotic readiness.

The relevance of this review is driven by the need to consolidate disparate data on the specifics of platelet abnormalities in various hematological pathologies and their contribution to cerebrovascular risk. Understanding these mechanisms is key to identifying patients at the highest risk of stroke and developing targeted preventive interventions. The aim of this work is to provide a comprehensive analysis of current knowledge on platelet dysfunction as a predictor of ischemic strokes in patients with MPNs, SCA, and PNH.

LITERATURE REVIEW

1. Platelet Physiology and Fundamentals of Dysfunction

Under normal conditions, platelets circulate in the bloodstream in a quiescent state. Their activation is a cascade process triggered by interaction with subendothelial structures (e.g., collagen) via GPIa/IIa and GPVI receptors, soluble agonists (ADP, thrombin, thromboxane A2), or shear stress [Varga-Szabo et al., 2008, p. 455]. A pivotal event is the conformational change in the GPIIb/IIIa receptor (integrin αIIbβ3), enabling it to bind fibrinogen and mediate platelet aggregation. Concurrently, the secretion of granule contents occurs (δ-granules with ADP, serotonin; α-granules with von Willebrand factor, P-selectin), amplifying and propagating the activation response.

Platelet dysfunction can manifest as hypofunction (increased bleeding) or hyperfunction (propensity for thrombosis). In the context of ischemic stroke, the focus is on the hyperfunctional state, which includes:

- Increased sensitivity to agonists: A lowered activation threshold in response to ADP, collagen, and epinephrine.
- Spontaneous activation: In vivo platelet activation without an apparent stimulus, reflected by elevated levels of circulating activation markers (P-selectin, activated GPIIb/IIIa).
- Impaired arachidonic acid metabolism: Enhanced synthesis of the proaggregatory and vasoconstrictive thromboxane A2.
- Procoagulant activity: Accelerated thrombin generation on the surface of activated platelets due to phosphatidylserine exposure ("flip-flop").

2. Platelet Dysfunction in Myeloproliferative Neoplasms (MPNs)

MPNs, particularly polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), are classic examples of diseases where thrombotic complications, including stroke, determine patient prognosis.

2.1. The Role of Thrombocytosis. For a long time, the primary cause of thrombosis in ET and PV was believed to be an elevated platelet count. However, large-scale studies, such as ECLAP (European Collaboration on Low-dose Aspirin in Polycythemia Vera), demonstrated a weak correlation between the degree of thrombocytosis and thrombosis risk [Marchioli et al., 2005, p. 87]. Moreover, some patients with extremely high platelet counts (>1,500,000/μL) may develop a hemorrhagic syndrome due to acquired von Willebrand syndrome, associated with the adsorption and clearance of von Willebrand factor multimers on the platelet surface. Thus, thrombocytosis is a necessary but insufficient condition for thrombosis, bringing qualitative anomalies to the forefront.

2.2. Qualitative Platelet Abnormalities in MPNs. Platelets in MPNs exhibit a spectrum of functional defects:

- Abnormal aggregation: Cases of both spontaneous in vitro aggregation and increased sensitivity to low doses of agonists (ADP, epinephrine), and paradoxically, a reduced response to some stimuli (ristocetin) have been described [Landolfi et al., 2008, p. 112].
- Granule and secretion defects: Reduced content of serotonin and ADP in δ-granules, as well as impaired secretion upon activation, are observed.

- Membrane receptor anomalies: Increased expression of the activated form of GPIIb/IIIa and decreased expression of the prostacyclin receptor (IP), a potent vasodilator and aggregation inhibitor [Arellano-Rodrigo et al., 2006, p. 623].
- Leukocyte activation and conjugate formation: Activated platelets form stable conjugates with leukocytes (primarily monocytes and neutrophils) via P-selectin. These conjugates possess heightened procoagulant and proinflammatory potential, contributing to endothelial injury [Falanga et al., 2007, p. 312].

2.3. The Pivotal Role of the JAK2 V617F Mutation. The discovery of the somatic mutation in the JAK2 tyrosine kinase gene (V617F) was a breakthrough in understanding MPN biology. This mutation is found in over 95% of PV patients and 50-60% of those with ET and PMF. Numerous studies have demonstrated that the presence of the JAK2 V617F mutation, particularly a high allele burden, is a powerful independent predictor of thrombotic complications, including stroke [Campbell et al., 2005, p. 2679]. Mechanisms linking the mutation to hypercoagulability include:

- Direct platelet activation: Constitutive activation of the JAK-STAT signaling pathway renders platelets hyperreactive.
- Leukocyte activation: Mutant leukocytes are in a state of constant activation, express tissue factor, and form conjugates with platelets.
- Endothelial dysfunction: The mutation can be found in endothelial cells, promoting a prothrombotic phenotype.

3. Platelet Dysfunction in Sickle Cell Anemia (SCA)

SCA is an inherited disorder characterized by the presence of pathological hemoglobin S (HbS), which polymerizes upon deoxygenation, leading to red blood cell deformation (sickling). Ischemic stroke is one of the most severe complications of SCA, affecting up to 11% of children and 24% of adults by age 45 [Ohene-Frempong et al., 1998, p. 134].

The pathogenesis of stroke in SCA is complex, and platelets play a critical role against a background of chronic hemolysis, endothelial dysfunction, and inflammation.

- Chronic in vivo platelet activation. Patients with SCA, even during steady state, exhibit elevated levels of platelet activation markers (P-selectin, soluble CD40 ligand) in plasma [Wun et al., 2001, p. 162]. This results from constant exposure to activating stimuli:
- Activated endothelium: Circulating sickle cells, hemolysis products (free heme, arginase), and proinflammatory cytokines cause damage and activation of the cerebral endothelium, increasing platelet adhesion.
- Activated leukocytes and erythrocytes: Platelets form aggregates with sickle erythrocytes and neutrophils, exacerbating microvascular occlusion.
- Impaired nitric oxide (NO) metabolism. Chronic hemolysis leads to NO depletion, a potent vasodilator and inhibitor of platelet activation. This promotes vasoconstriction and further platelet activation [Rother et al., 2005, p. 1653].

- Altered aggregability. Platelets from SCA patients demonstrate enhanced aggregation in response to ADP and collagen, correlating with the frequency of vaso-occlusive crises.

4. Platelet Dysfunction in Paroxysmal Nocturnal Hemoglobinuria (PNH)

PNH is a rare, acquired clonal disorder caused by a somatic mutation in the PIG-A gene, leading to a defect in glycosylphosphatidylinositol (GPI) anchor synthesis. Consequently, blood cells, including platelets, lack GPI-anchored proteins such as CD55 (DAF) and CD59 (MIRL), which protect cells from complement-mediated lysis.

The risk of thrombosis, including cerebral venous thrombosis and arterial strokes, is extremely high in PNH patients and is a leading cause of death. Platelet dysfunction in PNH has a unique mechanism:

- Paradoxical complement sensitivity. The deficiency of CD55 and CD59 makes platelets vulnerable to attack by the complement system. However, unlike erythrocytes, this does not always lead to their lysis. Sublytical exposure to the membrane attack complex (MAC) serves as a powerful activating stimulus for platelets [Wiedmer et al., 1993, p. 739]. The activated platelet exposes a procoagulant phosphatidylserine surface and secretes procoagulant microvesicles.
- Chronic in vivo activation. Patients with PNH experience constant complement activation, maintaining platelets in a state of readiness. Hemolytic episodes (e.g., during infections) further intensify this activation.
- Synergy with hemolysis. Free heme released during hemolysis is itself a proinflammatory and procoagulant agent, exacerbating endothelial dysfunction and creating a favorable background for platelet-mediated thrombosis.

DISCUSSION

The conducted analysis of the literature affirms that platelet dysfunction is a common pathogenic denominator linking various chronic blood disorders of different etiologies in the context of a high risk of ischemic stroke. However, the specific mechanisms of this dysfunction differ significantly, which has crucial implications for diagnosis and prevention.

In MPNs, the dominant factor is clonal proliferation driven by mutations in JAK2, CALR, or MPL genes. This results in the production of inherently "defective" platelets with an altered receptor apparatus and metabolism. The JAK2 V617F mutation acts not merely as a diagnostic marker but as a direct driver of hypercoagulability, affecting all myeloid lineage cells. This explains why thrombosis risk stratification in MPNs is now unthinkable without determining the molecular-genetic status.

In SCA, the primary event is erythrocyte pathology, and platelet dysfunction is secondary and reactive. It arises in response to chronic inflammation, endothelial dysfunction, and the constant "noise" of activating stimuli from damaged sickle cells. Here, the platelet acts as an amplifier and integrator of pathological signals circulating within the system. This underscores the importance of controlling not

only the platelet component but also the underlying disease (e.g., with hydroxyurea or transfusion programs).

In PNH, the mechanism is unique and linked to a defect in the innate complement defense system. Platelets in PNH are hostages of their own vulnerability: the complement system, a part of immune defense, becomes their constant activator. This fundamentally distinguishes PNH from MPNs and SCA and explains the high efficacy of complement inhibitor therapy (eculizumab), which, by blocking complement activation, not only halts hemolysis but also drastically reduces the frequency of thromboses.

An important aspect of the discussion is the challenge of antiplatelet therapy. The standard for primary thrombosis prevention in MPNs is low-dose aspirin, whose efficacy was proven in the ECLAP study [Landolfi et al., 2004, p. 114]. However, some patients exhibit "aspirin resistance," which may be related to ongoing platelet activation via JAK-STAT pathways independent of cyclooxygenase-1. In SCA, aspirin is also used, but its efficacy is less clear, and key roles in stroke prevention are held by transfusion programs or hydroxyurea. In PNH, antiplatelet agents are ineffective as they do not target the root cause—complement activation.

Thus, despite the common endpoint—ischemic stroke—the pathogenic pathways are distinct. This dictates the need for a personalized approach to risk assessment and the selection of preventive strategies, based on an understanding of the specifics of platelet dysfunction in each particular nosology.

RESULTS

Based on the systematization of literature data, key laboratory and molecular markers of platelet dysfunction associated with an increased risk of ischemic stroke in chronic blood disorders can be identified.

Table 1. Markers of Platelet Dysfunction and Their Prognostic Value in Various Chronic Blood Disorders.

Disease	Key Markers of Platelet Dysfunction	Association with Stroke Risk	Assessment Methods
Myeloproliferative Neoplasms	-Presence of **JAK2 V617F** mutation (especially high allele burden) -Increased spontaneous or agonist-induced aggregation - Increased **P-selectin (CD62P)** expression -Formation of platelet-leukocyte aggregates - Reduced response to aspirin	Strong direct correlation. JAK2 V617F is an independent risk factor.	PCR, allele burden; aggregometry (optical, impedance); flow cytometry; functional aspirin resistance tests.
Sickle Cell Anemia	-Elevated plasma levels	Correlates with the	ELISA; aggregometry;

Disease	Key Markers of Platelet Dysfunction	Association with Stroke Risk	Assessment Methods
	of **soluble P-selectin** and **sCD40L** -Enhanced aggregation with ADP/collagen -Formation of aggregates with neutrophils and sickle erythrocytes -Decreased nitric oxide (NO) levels	frequency of vaso-occlusive crises and cerebrovascular events.	flow cytometry; assessment of vasodilation.
Paroxysmal Nocturnal Hemoglobinuria	-Deficiency of **CD55** and **CD59** on the platelet membrane -Enhanced complement-induced activation (phosphatidylserine exposure) - Increased generation of procoagulant microvesicles	Extremely high risk, especially with a large clone size and during hemolysis.	Flow cytometry (FLAER); coagulometric assays; flow cytometry for microvesicles.

For a visual representation of the pathogenic mechanisms, the following scheme can be used:

Table 2. Comparative Characteristics of Approaches to Correcting Platelet Dysfunction and Preventing Stroke.

Disease	Primary Pathogenetic Mechanism	Main Stroke Prevention Methods Targeting Platelets	Efficacy
MPN	Clonal Hyperreactivity	-Low-dose Aspirin - Cytoreductive Therapy (hydroxyurea, interferon) for cell count control - JAK Inhibitors (ruxolitinib)	High for aspirin and cytoreduction. JAK inhibitors have demonstrated reduced thrombotic events.
SCA	Secondary Activation due to Inflammation & Hemolysis	-Hydroxyurea (lowers HbS, reduces inflammation) -Chronic Transfusion Programs -Aspirin (role less defined)	High for hydroxyurea and transfusions. Aspirin has an auxiliary role.
PNH	Complement-Mediated Activation	-Terminal Complement Inhibitors (eculizumab, ravulizumab) - Anticoagulants (if history of thrombosis) - Antiplatelets are ineffective	Very high for complement inhibitors (drastic reduction in thromboses).

CONCLUSION

1. Platelet dysfunction represents a universal and significant pathogenic factor contributing substantially to the development of ischemic strokes in patients with a wide spectrum of chronic blood disorders, including myeloproliferative neoplasms, sickle cell anemia, and paroxysmal nocturnal hemoglobinuria.

2. Despite the common endpoint, the molecular and cellular mechanisms underlying platelet hyperfunction are fundamentally distinct: clonal determinism in MPNs, secondary reactive activation in SCA, and complement-mediated activation in PNH.

3. Stroke risk assessment in this patient category should not be limited to platelet count. A comprehensive approach must be integrated into clinical practice, including the evaluation of platelet functional activity (aggregometry, flow cytometry for activation markers) and mandatory molecular-genetic testing (JAK2 V617F for MPNs, FLAER test for PNH).

4. The strategy for preventing cerebrovascular events must be etiotropic and personalized, targeting the correction of the primary dysfunction mechanism: cytoreduction and aspirin in MPNs; control of hemolysis and inflammation in SCA; complement inhibition in PNH.

5. Promising directions for future research include: investigating the role of novel mutations (CALR, MPL) in MPNs in modulating platelet function; searching for more effective antiplatelet agents that overcome "resistance"; and developing methods to correct endothelial dysfunction as a background for platelet hyperreactivity.

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