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AGE-RELATED CHANGES IN PLATELET FUNCTION AND THEIR IMPACT ON COGNITIVE DECLINE AND CEREBRAL MICROCIRCULATION

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ABSTRACT

Age-related alterations of the hemostatic system, particularly within the platelet component, have gained increasing scientific attention due to global population aging and the rising prevalence of cognitive impairment and dementia. Platelets, traditionally viewed as primary mediators of hemostasis, are now recognized as multifunctional circulating cells involved in inflammation, immune modulation, angiogenesis, and regulation of microcirculation, including within the cerebral vasculature. Accumulating evidence suggests that age-associated platelet hyperreactivity contributes to endothelial dysfunction, cerebral microthrombosis, chronic hypoperfusion, and neuroinflammation, all of which play central roles in cognitive decline and neurodegenerative disorders.

This narrative literature review aims to systematize and critically analyze current experimental and clinical data on age-related changes in platelet function and their contribution to impaired cerebral microcirculation and cognitive deterioration. Particular emphasis is placed on alterations in platelet adhesion, aggregation, secretion, receptor expression, and intracellular signaling pathways, as well as platelet interactions with endothelial cells and components of the neurovascular unit. Special attention is given to the involvement of platelets in vascular cognitive impairment, Alzheimer's disease, and cerebral small vessel disease. Understanding platelet-driven mechanisms in brain aging may open new avenues for preventive and therapeutic strategies targeting platelet activity in elderly populations.

KEY WORDS: Platelets; aging; cerebral microcirculation; cognitive decline; hemostasis; neurovascular unit; endothelial dysfunction; neuroinflammation.

INTRODUCTION

Population aging represents one of the most significant demographic challenges of the 21st century and is accompanied by a dramatic increase in age-related neurological disorders, including mild cognitive impairment, vascular dementia, and Alzheimer's disease. Cerebral hypoperfusion, microvascular dysfunction, and chronic neuroinflammation are widely recognized as central mechanisms underlying cognitive decline in older adults [Rossi, 2010, p. 12]. In parallel, aging is associated with profound changes in the hemostatic system, resulting in a prothrombotic phenotype.

While alterations in coagulation factors have been extensively studied, platelet dysfunction has emerged as a critical yet underappreciated contributor to age-related vascular pathology. Platelets are anucleate cell fragments derived from megakaryocytes that exhibit remarkable functional versatility. Beyond their classical role in thrombus formation, platelets actively interact with leukocytes, endothelial cells, and neural tissues, releasing a broad array of bioactive mediators, including cytokines, chemokines, growth factors, and neurotransmitters [Gawaz, 2004, p. 87].

The cerebral microcirculation is particularly vulnerable to subtle disturbances in blood flow and endothelial integrity. Even mild but chronic reductions in perfusion can lead to white matter damage, synaptic dysfunction, and progressive cognitive impairment [Iadecola, 2017, p. 145]. Given their central role in microvascular regulation, age-related changes in platelet function may represent a crucial mechanistic link between systemic aging and brain dysfunction.

LITERATURE REVIEW

1. Aging and Platelet Production

Aging is accompanied by quantitative and qualitative alterations in hematopoiesis. Hematopoietic stem cells demonstrate reduced regenerative capacity and a bias toward myeloid lineage differentiation, affecting megakaryopoiesis and platelet production. Several studies report increased mean platelet volume (MPV) in elderly individuals, a parameter associated with enhanced platelet reactivity and thrombotic risk [Michelson, 2011, p. 203]. Larger platelets contain higher granule content and display increased surface receptor density.

2. Age-Related Changes in Platelet Adhesion and Aggregation

Multiple clinical studies demonstrate enhanced platelet aggregation responses to agonists such as adenosine diphosphate (ADP), collagen, and thrombin in older adults [Davì, 2007, p. 56]. This hyperreactivity is partially explained by increased expression and activation of platelet surface glycoproteins, including GPIIb/IIIa and GPIb-IX-V complexes, which mediate fibrinogen and von Willebrand factor binding.

Additionally, age-associated oxidative stress alters platelet membrane fluidity and intracellular calcium homeostasis, further amplifying aggregation responses [Valko, 2007, p. 42]. Reduced sensitivity to endogenous platelet inhibitors, such as nitric oxide (NO) and prostacyclin (PGI_2), exacerbates this proaggregant phenotype.

3. Platelet Secretion and Proinflammatory Phenotype

Platelets from elderly individuals exhibit enhanced secretion of alpha- and dense-granule contents, including thromboxane A_2, serotonin, platelet-derived growth factor (PDGF), and soluble CD40 ligand (sCD40L). Elevated plasma levels of sCD40L are strongly associated with endothelial activation, vascular inflammation, and atherosclerosis progression [Henn, 2001, p. 211].

This proinflammatory platelet phenotype promotes leukocyte recruitment and amplifies neurovascular inflammation, contributing to blood–brain barrier (BBB) disruption.

4. Platelet–Endothelium Interactions in Cerebral Microcirculation

Endothelial dysfunction is a hallmark of vascular aging. Reduced bioavailability of NO and prostacyclin diminishes the antithrombotic properties of cerebral endothelium, facilitating platelet adhesion and microthrombus formation [Moncada, 1991, p. 98]. Activated platelets adhere to dysfunctional endothelium via P-selectin and integrin-mediated mechanisms, particularly within cerebral arterioles and capillaries.

Repeated episodes of platelet-mediated microvascular occlusion result in chronic cerebral hypoperfusion and focal ischemic injury, even in the absence of large-vessel disease.

5. Platelets and Cognitive Decline

Growing evidence links platelet hyperactivation to cognitive impairment and dementia. Patients with Alzheimer's disease exhibit increased platelet aggregation, altered APP (amyloid precursor protein) processing, and elevated circulating platelet-derived amyloid-β [Sevush, 1998, p. 64]. Platelets are considered a major peripheral source of amyloid-β, contributing to cerebral amyloid angiopathy.

Similarly, vascular cognitive impairment is strongly associated with markers of platelet activation and microvascular thrombosis [Pantoni, 2010, p. 221].

DISCUSSION

The data reviewed indicate that platelet aging is characterized by a shift toward a hyperreactive, proinflammatory, and prothrombotic phenotype. This shift is driven by intrinsic platelet alterations, endothelial dysfunction, oxidative stress, and impaired inhibitory signaling. In the cerebral circulation, these changes synergistically promote microthrombosis, BBB disruption, and neuroinflammation.

Platelet-derived mediators influence microglial activation and astrocytic function, linking systemic hemostatic aging to central nervous system inflammation. Thus, platelets act as critical effectors at the interface between vascular pathology and neurodegeneration [Iadecola, 2017, p. 145].

RESULTS

Table 1. Age-Related Changes in Platelet Function

Parameter	Young Adults	Elderly Individuals
Mean platelet volume	Normal	Increased
ADP-induced aggregation	Moderate	Enhanced
GPIIb/IIIa expression	Baseline	Upregulated
sCD40L secretion	Low	Elevated

Table 2. Platelet Activity and Cognitive Status

Indicator	Normal Cognition	Cognitive Decline
Thromboxane A_2	Normal	Increased
Cerebral microthrombosis	Rare	Frequent
Cerebral perfusion	Preserved	Reduced

Scheme 1. Platelet-Mediated Mechanisms of Cognitive Decline

Aging → Platelet hyperreactivity → Endothelial dysfunction and microthrombosis → Chronic cerebral hypoperfusion → Neuroinflammation → Cognitive decline.

CONCLUSION

Age-related changes in platelet function represent a crucial and often underestimated mechanism linking systemic aging to cerebral microvascular dysfunction and cognitive decline. Platelet hyperreactivity, enhanced secretion of proinflammatory mediators, and dysregulated interactions with the cerebral endothelium contribute to chronic hypoperfusion and neurodegeneration. Targeting platelet activation pathways may provide novel preventive and therapeutic strategies to preserve cognitive function in aging populations.

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