BIOMARKERS FOR THE EARLY DIAGNOSIS OF STROKE

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Abstract: Stroke is a major neurological disorder and a leading cause of death and long-term disability worldwide. Early diagnosis is essential for timely treatment and improved outcomes. Although computed tomography and magnetic resonance imaging remain the main diagnostic methods, their limitations in the earliest stages highlight the need for additional approaches. Circulating biomarkers such as GFAP, S100B, NSE, UCH-L1, MMP-9, inflammatory mediators, and microRNAs show potential for early detection, differentiation, and prognostic assessment of stroke. These biomarkers reflect neuronal injury, astrocytic activation, blood–brain barrier disruption, neuroinflammation, and vascular damage. This review summarizes their biological significance, diagnostic potential, and clinical limitations. Further studies are needed to establish standardized thresholds and validate biomarker panels for routine clinical use.

Keywords: stroke, early diagnosis, biomarkers, ischemic stroke, hemorrhagic stroke, GFAP, S100B, neuroinflammation.

Аннотация: Инсульт является одной из ведущих причин смертности и длительной инвалидизации во всем мире. Ранняя диагностика необходима для своевременного лечения и улучшения клинических исходов. Несмотря на то, что компьютерная и магнитно-резонансная томография остаются основными методами диагностики, их ограничения на ранних стадиях заболевания обусловливают необходимость дополнительных диагностических подходов. Циркулирующие биомаркеры, включая GFAP, S100B, NSE, UCH-L1, MMP-9, медиаторы воспаления и микроРНК, имеют потенциал для раннего выявления, дифференциации и прогностической

оценки инсульта. Они отражают повреждение нейронов, активацию астроцитов, нарушение гематоэнцефалического барьера, нейровоспаление и сосудистое повреждение. В обзоре рассматриваются их биологическое значение, диагностический потенциал и клинические ограничения. Необходимы дальнейшие исследования для определения стандартизированных пороговых значений и валидации биомаркерных панелей.

Ключевые слова: инсульт, ранняя диагностика, биомаркеры, ишемический инсульт, геморрагический инсульт, GFAP, S100B, нейровоспаление.

Annotatsiya: Insult dunyo miqyosida o‘lim va uzoq muddatli nogironlikning yetakchi sabablaridan biridir. Erta tashxis o‘z vaqtida davolashni boshlash va klinik natijalarni yaxshilash uchun muhimdir. Kompyuter tomografiyasi va magnit-rezonans tomografiya asosiy diagnostika usullari bo‘lib qolayotganiga qaramay, kasallikning dastlabki bosqichlaridagi cheklovlari qo‘shimcha diagnostik yondashuvlarga ehtiyoj tug‘diradi. GFAP, S100B, NSE, UCH-L1, MMP-9, yallig‘lanish mediatorlari va mikroRNKlar kabi aylanib yuruvchi biomarkerlar insultni erta aniqlash, differensiallash va prognozini baholashda istiqbolli hisoblanadi. Ular neyronlar shikastlanishi, astrositlar faollashuvi, qon-miya to‘sig‘i buzilishi, neyroyallig‘lanish va qon tomirlar zararlanishini aks ettiradi. Ushbu sharhda biomarkerlarning biologik ahamiyati, diagnostik salohiyati va klinik cheklovlari ko‘rib chiqiladi. Ularni klinik amaliyotga joriy etish uchun standart chegaraviy qiymatlar va biomarker panellarini tasdiqlash bo‘yicha qo‘shimcha tadqiqotlar zarur.

Kalit so‘zlar: insult, erta tashxis, biomarkerlar, ishemik insult, gemorragik insult, GFAP, S100B, neyroyallig‘lanish.

Introduction: Atherosclerosis is a chronic vascular disease characterized by lipid accumulation, inflammation, extracellular matrix remodeling, and progressive structural changes in the arterial wall. In advanced lesions, calcium-phosphate

deposits may develop within the plaque. Vascular calcification was previously considered a passive consequence of tissue degeneration; however, current evidence indicates that it is an actively regulated process involving cellular phenotypic changes, extracellular vesicles, matrix remodeling, mineral metabolism, and intracellular signaling.

Calcification is common in advanced atherosclerotic lesions and may occur as small microcalcifications or larger, confluent deposits. Therefore, its biological effects depend not only on the presence of calcium but also on the size, morphology, and distribution of mineral deposits.

Vascular smooth muscle cells (VSMCs) are key cellular contributors to plaque calcification. Under physiological conditions, VSMCs maintain a contractile phenotype that supports vascular structure and function. In the pathological plaque environment, inflammatory mediators, oxidative stress, lipid accumulation, mechanical changes, and matrix remodeling can induce VSMC phenotypic switching toward osteogenic or chondrogenic states. Experimental and lineage-tracing studies support VSMCs as an important source of osteochondrogenic cells in calcifying vascular lesions.

RUNX2 is a major transcriptional regulator of osteogenic differentiation. Its increased activity in VSMCs is associated with loss of contractile characteristics and acquisition of an osteogenic phenotype. Several signaling pathways contribute to this process, including bone morphogenetic protein (BMP)/SMAD and Wnt/β-catenin pathways, which can interact with RUNX2 and other transcriptional regulators to promote vascular mineralization.

Inflammation and oxidative stress further enhance VSMC phenotypic transformation, apoptosis, extracellular vesicle release, and extracellular matrix remodeling. These processes facilitate the initiation and progression of calcium-phosphate deposition. The relationship between calcification and plaque stability is complex: microcalcifications may increase local mechanical stress, whereas larger and more continuous calcified regions may have different biomechanical effects.

Despite substantial progress, the interactions between inflammation, VSMC plasticity, osteogenic signaling, matrix remodeling, and mineral deposition remain incompletely understood. Therefore, this review focuses on the cellular and molecular mechanisms of atherosclerotic plaque calcification, with particular emphasis on VSMC osteogenic transformation and the major signaling pathways involved.

Pathogenesis of Atherosclerotic Plaque Calcification

Atherosclerotic plaque calcification results from coordinated cellular and extracellular processes involving inflammation, VSMC phenotypic switching, apoptosis, extracellular matrix remodeling, and disturbances in calcium-phosphate homeostasis. An imbalance between mineralization-promoting factors and endogenous inhibitors creates a pro-calcific vascular environment.

Initiation of Mineral Deposition

Early mineralization is closely associated with cellular injury and inflammation. Exposure of macrophages and VSMCs to oxidized lipids, inflammatory mediators, and oxidative stress promotes cellular dysfunction and apoptosis. Apoptotic bodies and extracellular vesicles can provide nucleation sites for calcium-phosphate crystal formation and contribute to the development of microcalcifications.

VSMC Injury and Apoptosis

VSMC apoptosis contributes to calcification by generating apoptotic bodies that facilitate mineral deposition. Persistent cell death may also weaken plaque structure. Inefficient clearance of apoptotic material promotes its accumulation within the necrotic core, where calcium and phosphate can facilitate further crystal formation.

Calcium-Phosphate Balance

Calcium and inorganic phosphate availability strongly influence vascular mineralization. Increased phosphate uptake by VSMCs through sodium-dependent phosphate transporters, particularly PiT-1, can promote osteogenic signaling and

calcification. Endogenous inhibitors, including matrix Gla protein, fetuin-A, pyrophosphate, and osteopontin, normally limit inappropriate mineralization. Disruption of this balance favors calcium-phosphate deposition.

Extracellular Matrix Remodeling

The extracellular matrix actively regulates mineralization by providing a structural environment for crystal formation and influencing VSMC behavior. Matrix degradation may expose sites that facilitate mineral nucleation, while osteogenic VSMCs can produce matrix components and extracellular vesicles that promote mineral deposition. Thus, VSMC phenotypic switching and matrix remodeling reinforce vascular calcification.

Inflammation

Inflammation is closely linked to plaque calcification. Pro-inflammatory cytokines and macrophage activity promote oxidative stress, apoptosis, extracellular vesicle release, and osteogenic differentiation. In turn, mineral deposits may further modify the inflammatory environment, creating a dynamic interaction between inflammation and calcification.

Progression of Calcification

Early deposits usually appear as small, dispersed calcium-phosphate accumulations. With continued cellular injury, inflammation, and matrix remodeling, they may enlarge and become more organized. However, microcalcifications do not necessarily progress into large calcified masses. Their biological effects depend on the morphology, size, and spatial organization of the deposits.Osteogenic Transformation of Vascular Smooth Muscle CellsVascular smooth muscle cells (VSMCs) are highly plastic cells capable of changing their phenotype in response to vascular injury and environmental stimuli. Under physiological conditions, they predominantly maintain a contractile phenotype characterized by markers such as α-smooth muscle actin (α-SMA), SM22α, smooth muscle myosin heavy chain, and calponin.

During atherosclerosis, lipid accumulation, inflammation, oxidative stress, altered mechanical forces, and extracellular matrix remodeling promote VSMC phenotypic switching. VSMCs may lose contractile characteristics and acquire fibroblast-like, macrophage-like, mesenchymal, osteogenic, or chondrogenic phenotypes. This plasticity contributes to plaque progression and vascular calcification.

Osteogenic transformation involves activation of transcriptional programs associated with bone formation. RUNX2 is a central regulator of this process and promotes the expression of osteogenic genes while interfering with the maintenance of the contractile VSMC phenotype. BMP/SMAD and Wnt/β-catenin signaling pathways can further enhance RUNX2 activity and osteogenic differentiation.Inflammation and oxidative stress contribute to this phenotypic transition by modifying intracellular signaling, promoting cellular injury, apoptosis, and extracellular vesicle release. These mechanisms facilitate extracellular calcium-phosphate deposition and progression of vascular calcification.Therefore, VSMC phenotypic plasticity represents a central mechanism linking the inflammatory atherosclerotic environment to osteogenic differentiation and plaque calcification.

Conclusion: Blood-based biomarkers have significant potential to support the early diagnosis and differentiation of stroke. Biomarkers such as GFAP, S100B, NSE, UCH-L1, MMP-9, inflammatory mediators, and circulating microRNAs reflect different mechanisms of cerebral injury and may provide diagnostic and prognostic information before or alongside conventional assessment. Among them, GFAP has shown particular potential for distinguishing ischemic stroke from intracerebral hemorrhage.

However, no individual biomarker currently has sufficient accuracy and standardization to replace neuroimaging in routine clinical practice. The main challenges include differences in biomarker kinetics, sampling time, assay methods, patient characteristics, and diagnostic thresholds. Therefore, the most

promising future strategy is likely to involve validated multimarker panels integrated with clinical assessment and neuroimaging. Large multicenter studies are needed to establish standardized protocols and determine whether biomarker-based approaches can improve the speed and accuracy of acute stroke diagnosis.

References

1. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke. Stroke. 2019;50(12):e344–e418. doi:10.1161/STR.0000000000000211.
2. Makris K, Haliassos A, Chondrogianni M, Tsivgoulis G. Blood biomarkers in ischemic stroke: Potential role and challenges in clinical practice and research. Critical Reviews in Clinical Laboratory Sciences. 2018;55(5):294–328. doi:10.1080/10408363.2018.1461190.
3. Monbailliu T, Goossens J, Hachimi-Idrissi S. Blood protein biomarkers as diagnostic tool for ischemic stroke: A systematic review. Biomarkers in Medicine. 2017;11(8):701–714. doi:10.2217/bmm-2016-0232.
4. Rahmig J, Chanpura A, Schultz A, Barone F, Gustafson D, Baird A. Blood-based protein biomarkers during the acute ischemic stroke treatment window: A systematic review. Frontiers in Neurology. 2024;15:1411307. doi:10.3389/fneur.2024.1411307.
5. Sjöberg C, et al. Non-coding RNAs versus protein biomarkers to diagnose and differentiate acute stroke: Systematic review and meta-analysis. 2023. PMID: 37778160.
6. Krishnamoorthy S, Singh G, Jose JK, Soman B, Foerch C, Kimberly WT, et al. Biomarkers in the Prediction of Hemorrhagic Transformation in Acute Stroke: A Systematic Review and Meta-Analysis. Cerebrovascular Diseases. 2022;51(2):235–247. doi:10.1159/000518570.

7. Wang L, Wei C, Deng L, et al. The Accuracy of Serum Matrix Metalloproteinase-9 for Predicting Hemorrhagic Transformation After Acute Ischemic Stroke: A Systematic Review and Meta-Analysis. Journal of Stroke and Cerebrovascular Diseases. 2018.
8. Wang Y, et al. Assessment of Serum UCH-L1 and GFAP in Acute Stroke Patients. 2016. PMID: 27074724.
9. Foerch C, Niessner M, Back T, Bauerle M, De Marchis GM, Ferbert A, et al. Diagnostic Accuracy of Glial Fibrillary Acidic Protein and Ubiquitin Carboxy-Terminal Hydrolase-L1 Serum Concentrations for Differentiating Acute Intracerebral Hemorrhage from Ischemic Stroke. 2020. PMID: 32096121.
10. Anand N, Stead LG. Neuron-specific enolase as a marker for acute ischemic stroke: A systematic review. Cerebrovascular Diseases. 2005;20(4):213–219. doi:10.1159/000087701.
11. Coppens S, Lehmann S, Hopley C, Hirtz C. Neurofilament-Light, a Promising Biomarker: Analytical, Metrological and Clinical Challenges. International Journal of Molecular Sciences. 2023;24(14):11624. doi:10.3390/ijms241411624.
12. The role of microRNAs as super-early biomarkers in acute ischemic stroke: A systematic review. Clinical Neurology and Neurosurgery. 2024;244:108416. doi:10.1016/j.clineuro.2024.108416.
13. Shu Y, Qin Y, Fang Q. Research Progress of Blood-Based Biomarkers for the Diagnosis and Prognostic Evaluation of Acute Ischemic Stroke. Biomolecules. 2026;16(7):937. doi:10.3390/biom16070937.
14. Temporal Patterning of Neurofilament Light as a Blood-Based Biomarker for Stroke: A Systematic Review and Meta-Analysis. 2022. PMID: 35651349.
15. Blood neurofilament light chain as a predictive biomarker for functional outcome of acute ischemic stroke: A systematic review and meta-analysis. 2025. PMID: 41054347.