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脑小血管病与炎症的密切关系

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摘　要

脑小血管病近年来发病率逐年增加，造成了社会巨大的经济负担，与年龄相关的CSVD亦在逐年上升，最常见的表现是脑卒中及认知障碍。临床前研究和临床研究均提示脑小血管病与炎症存在一定的相关关系，因此本文综述了炎症和CSVD病理生理进展的最新研究。

关键词

脑小血管病，炎症

The Close Relationship between Cerebral Small Blood Vessel Disease and Inflammation

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Abstract

In recent years, the incidence of cerebral small vascular disease has increased year by year, causing a huge economic burden on the society. The age-related CSVD is also increasing year by year. The most common manifestations are stroke, cognitive impairment, and even dementia. Both preclinical studies and clinical research suggest that there is a correlation between cerebral small vessel disease and inflammation. Based on this, this paper reviews the latest studies on the pathophysiology of inflammation and CSVD, and explores the potential link between inflammation and age-related CSVD, in order to provide new ideas for further research in diagnosis and treatment.

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Keywords

Cerebral Small Blood Vessel Disease, Inflammation

1. 引言

脑小血管病(CSVD)是指各种病因影响直径 ＜400 微米的小动脉及其远端分支、微动脉、毛细血管和微静脉和小静脉所导致一系列临床、影像、病理综合征[1]。CSVD 的主要临床表现为脑卒中、认知能力下降、痴呆、精神障碍、步态异常、尿失禁[2]等，CSVD 的神经影像学特征包括近期皮质下小梗死、腔隙性梗死、白质高信号、扩大的血管周围间隙、脑微出血和脑萎缩[3]。

近年来，伴随着全球预期寿命的稳步增长，与年龄相关的 CSVD 发病率也在增加，数据表明约 5%的 50 岁人群和几乎所有 90 岁以上的人都受到影响，给社会造成了巨大的经济负担[4]。欧洲小脑血管病专家组根据脑血管病理改变提出 CSVD 的分类如下：动脉粥样硬化、散发性和遗传性脑淀粉样血管病、与脑淀粉样血管病不同的遗传性或遗传性小血管疾病、炎症性和免疫介导的小血管疾病、静脉胶原病、放疗后血管病变等其他小血管疾病[5]。虽然目前发现可改变危险因素是高血压、糖尿病、高脂血症、吸烟[6]，阻塞性睡眠呼吸暂停[7]，社会经济和教育状况[8]，但年龄和遗传因素是 CSVD 的不可改变的危险因素[9] [10] [11]。血脑屏障是一种内皮细胞的紧密调节合胞体，具有低的跨细胞和细胞旁转运特性，围绕脑血管，保护脆弱的神经元微环境免受神经毒性物质的影响。星形胶质细胞、周细胞、小胶质细胞和基底膜的相互作用使内皮运输受到严格调节，共同形成构成血脑屏障(BBB)的神经血管单元。星形胶质细胞和周细胞直接包围内皮细胞，不仅有助于将血液供应与代谢需求联系起来，还分泌许多增强和维持血脑屏障完整性的分子[12] [13] [14] [15]。小胶质细胞是神经血管单位的一部分，它们的消融可通过释放细胞因子或活性氧对血脑屏障的完整性产生不利影响[16] [17]。有研究发现全身炎症可诱导脑内小胶质细胞向脑血管系统迁移，这些小胶质细胞最初维持血脑屏障的完整性，但随后吞噬星形细胞的末端足，导致血脑屏障功能障碍[18]。而内皮功能障碍和随后血脑屏障(BBB)通透性增加与 CSVD 的发展有关，这得到了实验研究[11] [19] [20] [21]、神经病理学研究[21] [22] [23]和影像学研究[6] [24] [25]的支持。此外，先前的一项研究表明，血管炎症标志物与 CSVD 之间有很强的相关性，尤其是在老年急性卒中的 CSVD 患者中[26]。因此本文探讨了炎症与年龄相关性 CSVD 之间的潜在联系。

炎症是免疫系统慢性生理刺激的长期结果，具有多种细胞和分子机制，包括细胞衰老、免疫衰老、线粒体功能障碍、自噬缺陷、过度炎症和肠道微生物群失调。线粒体功能障碍和自噬缺陷有利于多种炎症途径的激活。例如，自噬缺陷促进了功能失调的线粒体的积累，导致大量线粒体 DNA (mtDNA)直接释放到细胞质中，诱导天胱蛋白酶-1 的激活和随后的 IL-1β3 的产生[27] [28]。此外，线粒体是调节细胞内钙库和活性氧(ROS)水平的信号中枢，这两种物质都是经典的炎症介质，线粒体和内质网接触位点的维持通过平衡细胞内钙库和调节自噬诱导来调节白细胞迁移和淋巴细胞活化[29]。在衰老的氧化炎症理论中，有人提出累积的 mtDNA 突变会破坏线粒体呼吸链，导致线粒体 ROS (mtROS)的过度产生。反过来，这加速了 mtDNA 新突变的出现(导致细胞衰老)，并加剧了炎症过程。此外，衰老导致 ROS 和炎症介质的进一步产生，即 oxi 炎症衰老，形成恶性循环[29]。

2. 临床前证据

一则关于 CSVD 动物模型的研究提示，炎症和内皮细胞(EC)功能障碍不仅是疾病的关键致病标志物，而且实际上可能先于 CSVD 的发展。利用大鼠双侧颈总动脉闭塞创作出 CSVD 患者低灌注的模型。使用该模型的研究表明，小胶质细胞活化增加了 10 倍，少突胶质细胞密度增加了一倍[30]。Jalal 等人在自发性高血压易中风大鼠(SHRSP)模型中使用单侧颈动脉闭塞来解释相关的合并症，并发现基质金属肽酶-9 (MMP-9)上调，伴有血脑屏障渗漏[31]。对未经手术的自发性高血压大鼠(SHR)模型的研究表明，仅高血压就足以引发神经炎症并引发 CSVD，这可能代表了一种更准确的人类 CSVD 模型。到 6 个月大时，SHR 大鼠表现出白质体积、小胶质细胞活化和 IL-1b 产生的减少，为炎症作为 CSVD 关键因素提供了证据[32]。

3. 临床证据

经 Shuling Wan 等人的统计，我们发现了一些炎症指标，一部分是系统性炎症指标，一部分是血管炎症或内皮功能障碍标志物。系统性炎症指标包括 C 反应蛋白、血清淀粉样蛋白、纤维蛋白原、细胞因子，血管炎症和内皮功能障碍标志物包括粘附分子、止血因子、同型半胱氨酸[33]。一方面，受促炎细胞因子的调控，最显著的是 IL-6，其次是 IL-1 和肿瘤坏死因子 α，血浆 CRP 通过降低内皮一氧化氮合酶(eNOS)的表达和生物活性，减少一氧化氮(NO)的产生，增加血管收缩剂和粘附分子(如 ICAM-1、VCAM-1 和 e-选择素)的释放，对内皮细胞(ECs)产生直接影响，从而在内皮功能障碍中发挥重要作用[34] [35]。血清淀粉样蛋白可刺激血管细胞表达细胞因子、趋化因子、粘附分子(如 ICAM-1、VCAM-1 和 e-选择素)和基质金属蛋白酶(MMPs)，从而产生全身炎症[36]。炎症可引起外周血纤维蛋白原高水平的释放[37]，纤维蛋白原大量释放可导致血浆粘度和红细胞聚集增加，血小板血栓形成和血管反应性增强，EC 层完整性破坏，导致血管功能障碍[38] [39] [40] [41]。细胞因子家族也在多种在炎症中起重要作用。包括上游炎症细胞因子 IL-6，多效性细胞因子 TNF-α，属于肿瘤坏死因子受体超家族的骨保护素(OPG)，内皮细胞特异生长因子：血管内皮生长因子(Vascular endothelial growth factor, VEGF)。IL-6 促进肝脏下游急性期反应物的产生，在炎症反应中起核心作用[26]。TNF-α 这种促炎和组织破坏细胞因子对少突胶质细胞有毒，从而介导髓鞘损伤和白质变性[42]。骨保护素与 NFκB 配体受体激活因子(RANKL)和肿瘤坏死因子相关凋亡诱导配体(TRAIL)结合，从而抑制其促炎和促凋亡信号通路的激活[43]。动物研究表明，VEGF 表达增加与血脑屏障通透性增加相关，导致血管源性水肿和血源性物质渗漏到脑实质[44] [45]。另一方面，细胞因子信号触发的局部血管内皮异常或持续激活可导致粘附分子的过度表达，进而促进白细胞的募集、粘附和浸润，从而损害血管和局部组织[46]。例如，E-和 p-选择素是粘附分子选择素家族的成员，可促进白细胞滚动并可逆粘附到血管内皮[46] [47] [48]。内皮细胞激活时，储存在血小板 α-颗粒和内皮细胞 webel-palade 小体(WPBs)中的止血因子 vWF 可释放到血浆和基底膜中，通过介导血小板粘附于受损和活化的血管，形成血栓破坏内皮细胞[49]。

与年龄相关的 CSVD 亚型包括深穿动脉病变(DPA)和 β-淀粉样蛋白(Aβ)相关的脑淀粉样血管病变(CAA)。区域分析显示，血管炎症标志物往往与 DPA (如基底神经节)有关，而全身炎症似乎与 CAA (如半卵圆中心)有关。除此以外，纵向调查表明，全身炎症因子的基线表达水平可以预测随后 CSVD 的严重程度[50]。

4. 影像学证据

一项横断面研究表明，在以社区为基础的日本老年人中，血浆纤维蛋白原水平与更高级别的 WMH 相关，并且纤维蛋白原和 WMH 之间存在独立关联[51]。Fornage 等人在心血管健康研究中发现白人血浆 CRP 水平较高与 WMH 风险较高之间存在显著关联[52]。Mitaki 等人发现，hs-CRP 较高的受试者有更多

的腔隙性梗死(p = 0.02)和 CMBs (p = 0.03)，以及更严重的 DWMH (p = 0.04)和室周高信号(PVH) (p = 0.04) [53]。Hilal 等人表明，在 2814 名平均年龄为 56.9 岁的参与者中，较高的 CRP 水平与较大的 WMHV 有关 [54]。Koh 等人在 206 例首次急性 LS 患者中发现，有微出血患者的 CRP 水平明显高于无微出血患者(0.93 ± 0.97 对 0.52 ± 0.31，p = 0.047) [55]。Noz 等人表明，在患有轻度至重度 CSVD 的老年受试者中，循环高敏 IL-6 (hsIL-6)在 2006 年和 2015 年基线时与 WMH 高度相关[56]。张等研究表明，阿尔茨海默病(AD)患者 VEGF 水平升高与 CMBs 的存在显著且独立相关。在控制混杂因素后，10 的 OR (95%CI) CMBs 存在时 VEGF 水平的增加为 2.37 (1.53~4.02) pg/ml (p = 0.004)。多变量回归分析进一步证明了临床因素和 VEGF 水平的组合与 CMBs 数量之间的显著相关性(p < 0.001；调整后的 R2 总计 = 0.312) [45]。Framingham 心脏研究发现，ICAM-1 (OR 1.7, 95% CI 1.1~2.5; p = 0.02)和脂蛋白相关磷脂酶 A2 (Lp-PLA2)质量(OR 1.5, 95% CI 1.1~2.1; p = 0.01)与广泛的 WMH 和/或 SCIs 呈正相关[45]。几项研究清楚地表明，在 CSVD 患者中，tHcy 水平与 MRI 病变的严重程度之间存在正相关。Vermeer 等人研究表明，tHcy 水平与 SBI 和 WMH 相关，它们相互独立，与其他心血管风险因素无关。受试者在 tHcy 每 SD 增加时发生 SBI 的可能性增加 24% (95% CI 为 6%~45%) [57]。Pavlovic 及其同事表明，塞尔维亚 SVD 患者的 tHcy 水平升高与 WMH 的严重程度呈正独立相关[58]。Gao 等研究表明，在急性缺血性脑卒中患者(平均年龄 58.9 岁)中 ± 11.9 年；女性，31.6%)，血浆 tHcy 水平升高与 WMHs 的严重程度显著且独立相关[59]。Altendahl 等人分别在 Mark VCID 研究和 ASPIRE 研究队列的两个不同人群中确定了以 IL-18 为中心的全身炎症网络与先行和显性白质损伤之间的横断面关系，炎症综合评分(ICS)是炎症标志物(髓过氧化物酶[MPO]、生长分化因子 15 [GDF-15]、晚期糖基化终产物受体[RAGE]、ST2、白细胞介素-18 [IL18]和单核细胞趋化蛋白-1 [MCP-1])的综合测量，与 log WMH (β = 0.222, p = 0.013)和 DTI FW (β = 0.3, p = 0.01)显著相关[60]。

5. 总结

本文虽然没有把所有关于炎症生物标志物与 CSVD MRI 特征之间关系的研究都包括在内，但炎症在年龄相关 CSVD 中的作用是未来诊断或治疗干预的新的方向，而且随着先进 MRI 技术的发展，CSVD 的病理机制可能会得到进一步揭示，未来 CSVD 的早期诊断甚至逆转或将成为可能。

参考文献

[1] Wardlaw, J.M., Smith, C. and Dichgans, M. (2013) Mechanisms of Sporadic Cerebral Small Vessel Disease: Insights from Neuroimaging. *The Lancet Neurology*, **12**, 483-497. https://doi.org/10.1016/S1474-4422(13)70060-7

[2] Li, Q., *et al.* (2018) Cerebral Small Vessel Disease. *Cell Transplantation*, **27**, 1711-1722. https://doi.org/10.1177/0963689718795148

[3] Wardlaw, J.M., *et al.* (2013) Neuroimaging Standards for Research into Small Vessel Disease and Its Contribution to Ageing and Neurodegeneration. *The Lancet Neurology*, **12**, 822-838. https://doi.org/10.1016/S1474-4422(13)70124-8

[4] Cannistraro, R.J., *et al.* (2019) CNS Small Vessel Disease: A Clinical Review. *Neurology*, **92**, 1146-1156. https://doi.org/10.1212/WNL.0000000000007654

[5] Pantoni, L. (2010) Cerebral Small Vessel Disease: from Pathogenesis and Clinical Characteristics to Therapeutic Challenges. *The Lancet Neurology*, **9**, 689-701. https://doi.org/10.1016/S1474-4422(10)70104-6

[6] Wang, Z., *et al.* (2021) Risk Factors of Cerebral Small Vessel Disease: A Systematic Review and Meta-Analysis. *Medicine* (*Baltimore*), **100**, e28229. https://doi.org/10.1097/MD.0000000000028229

[7] Kim, H., *et al.* (2013) Obstructive Sleep Apnea as a Risk Factor for Cerebral White Matter Change in a Middle-Aged and Older General Population. *Sleep*, **36**, 709-715. https://doi.org/10.5665/sleep.2632

[8] Backhouse, E.V., *et al.* (2017) Early Life Risk Factors for Cerebrovascular Disease: A Systematic Review and Meta-Analysis. *Neurology*, **88**, 976-984. https://doi.org/10.1212/WNL.0000000000003687

[9] De Leeuw, F.E., *et al.* (2001) Prevalence of Cerebral White Matter Lesions in Elderly People: A Population Based Magnetic Resonance Imaging Study. The Rotterdam Scan Study. *Journal of Neurology, Neurosurgery and Psychiatry*, **70**, 9-14. https://doi.org/10.1136/jnnp.70.1.9

[10] Hilal, S., *et al.* (2017) Prevalence, Risk Factors and Consequences of Cerebral Small Vessel Diseases: Data from Three Asian Countries. *Journal of Neurology, Neurosurgery and Psychiatry*, **88**, 669-674. https://doi.org/10.1136/jnnp-2016-315324

[11] Poels, M.M., *et al.* (2010) Prevalence and Risk Factors of Cerebral Microbleeds: An Update of the Rotterdam Scan Study. *Stroke*, **41**, S103-S106. https://doi.org/10.1161/STROKEAHA.110.595181

[12] Obermeier, B., Daneman, R. and Ransohoff, R.M. (2013) Development, Maintenance and Disruption of the Blood-Brain Barrier. *Nature Medicine*, **19**, 1584-1596. https://doi.org/10.1038/nm.3407

[13] Keaney, J. and Campbell, M. (2015) The Dynamic Blood-Brain Barrier. *The FEBS Journal*, **282**, 4067-4079. https://doi.org/10.1111/febs.13412

[14] Kleinberger, G., *et al.* (2017) The FTD-Like Syndrome Causing TREM2 T66M Mutation Impairs Microglia Function, Brain Perfusion, and Glucose Metabolism. *The EMBO Journal*, **36**, 1837-1853. https://doi.org/10.15252/embj.201796516

[15] Liebner, S., *et al.* (2018) Functional Morphology of the Blood-Brain Barrier in Health and Disease. *Acta Neuropathologica*, **135**, 311-336. https://doi.org/10.1007/s00401-018-1815-1

[16] Dudvarski Stankovic, N., *et al.* (2016) Microglia-Blood Vessel Interactions: A Double-Edged Sword in Brain Pathologies. *Acta Neuropathologica*, **131**, 347-363. https://doi.org/10.1007/s00401-015-1524-y

[17] Varatharaj, A. and Galea, I. (2017) The Blood-Brain Barrier in Systemic Inflammation. *Brain, Behavior, and Immunity*, **60**, 1-12. https://doi.org/10.1016/j.bbi.2016.03.010

[18] Haruwaka, K., *et al.* (2019) Dual Microglia Effects on Blood Brain Barrier Permeability Induced by Systemic Inflammation. *Nature Communications*, **10**, Article No. 5816. https://doi.org/10.1038/s41467-019-13812-z

[19] Jalal, F.Y., *et al.* (2015) Hypoxia-Induced Neuroinflammatory White-Matter Injury Reduced by Minocycline in SHR/SP. *Journal of Cerebral Blood Flow & Metabolism*, **35**, 1145-1153. https://doi.org/10.1038/jcbfm.2015.21

[20] Ueno, M., *et al.* (2002) Blood-Brain Barrier Disruption in White Matter Lesions in a Rat Model of Chronic Cerebral Hypoperfusion. *Journal of Cerebral Blood Flow & Metabolism*, **22**, 97-104. https://doi.org/10.1097/00004647-200201000-00012

[21] Tomimoto, H., *et al.* (1996) Alterations of the Blood-Brain Barrier and Glial Cells in White-Matter Lesions in Cerebrovascular and Alzheimer's Disease Patients. *Stroke*, **27**, 2069-2074. https://doi.org/10.1161/01.STR.27.11.2069

[22] Forsberg, K.M.E., *et al.* (2018) Endothelial Damage, Vascular Bagging and Remodeling of the Microvascular Bed in Human Microangiopathy with Deep White Matter Lesions. *Acta Neuropathologica Communications*, **6**, Article No. 128. https://doi.org/10.1186/s40478-018-0632-z

[23] Young, V.G., Halliday, G.M. and Kril, J.J. (2008) Neuropathologic Correlates of White Matter Hyperintensities. *Neurology*, **71**, 804-811. https://doi.org/10.1212/01.wnl.0000319691.50117.54

[24] Wardlaw, J.M., *et al.* (2009) Lacunar Stroke Is Associated with Diffuse Blood-Brain Barrier Dysfunction. *Annals of Neurology*, **65**, 194-202. https://doi.org/10.1002/ana.21549

[25] Topakian, R., *et al.* (2010) Blood-Brain Barrier Permeability Is Increased in Normal-Appearing White Matter in Patients with Lacunar Stroke and Leucoaraiosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **81**, 192-197. https://doi.org/10.1136/jnnp.2009.172072

[26] Held, C., *et al.* (2017) Inflammatory Biomarkers Interleukin-6 and C-Reactive Protein and Outcomes in Stable Coronary Heart Disease: Experiences from the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) Trial. *Journal of the American Heart Association*, **6**, e005077. https://doi.org/10.1161/JAHA.116.005077

[27] Nakahira, K., *et al.* (2011) Autophagy Proteins Regulate Innate Immune Responses by Inhibiting the Release of Mitochondrial DNA Mediated by the NALP3 Inflammasome. *Nature Immunology*, **12**, 222-230. https://doi.org/10.1038/ni.1980

[28] Oka, T., *et al.* (2012) Mitochondrial DNA That Escapes from Autophagy Causes Inflammation and Heart Failure. *Nature*, **485**, 251-255. https://doi.org/10.1038/nature10992

[29] Martinvalet, D. (2018) The Role of the Mitochondria and the Endoplasmic Reticulum Contact Sites in the Development of the Immune Responses. *Cell Death & Disease*, **9**, Article No. 336. https://doi.org/10.1038/s41419-017-0237-7

[30] Farkas, E., *et al.* (2004) Experimental Cerebral Hypoperfusion Induces White Matter Injury and Microglial Activation in the Rat Brain. *Acta Neuropathologica*, **108**, 57-64. https://doi.org/10.1007/s00401-004-0864-9

[31] Jalal, F.Y., *et al.* (2012) Myelin Loss Associated with Neuroinflammation in Hypertensive Rats. *Stroke*, **43**, 1115-1122. https://doi.org/10.1161/STROKEAHA.111.643080

[32] Kaiser, D., *et al.* (2014) Spontaneous White Matter Damage, Cognitive Decline and Neuroinflammation in Mid-

dle-Aged Hypertensive Rats: An Animal Model of Early-Stage Cerebral Small Vessel Disease. *Acta Neuropathologica Communications*, **2**, Article No. 169. https://doi.org/10.1186/s40478-014-0169-8

[33] Wan, S., *et al.* (2023) Plasma Inflammatory Biomarkers in Cerebral Small Vessel Disease: A Review. *CNS Neuroscience & Therapeutics*, **29**, 498-515. https://doi.org/10.1111/cns.14047

[34] Ling, C., *et al.* (2021) The Effect of Race and Shear Stress on CRP-Induced Responses in Endothelial Cells. *Mediators of Inflammation*, **2021**, Article ID: 6687250. https://doi.org/10.1155/2021/6687250

[35] Pasceri, V., Willerson, J.T. and Yeh, E.T. (2000) Direct Proinflammatory Effect of C-Reactive Protein on Human Endothelial Cells. *Circulation*, **102**, 2165-2168. https://doi.org/10.1161/01.CIR.102.18.2165

[36] Nishida, E., *et al.* (2016) Serum Amyloid A Promotes E-Selectin Expression via Toll-Like Receptor 2 in Human Aortic Endothelial Cells. *Mediators of Inflammation*, **2016**, Article ID: 7150509. https://doi.org/10.1155/2016/7150509

[37] Eber, B. and Schumacher, M. (1993) Fibrinogen: Its Role in the Hemostatic Regulation in Atherosclerosis. *Seminars in Thrombosis and Hemostasis*, **19**, 104-107. https://doi.org/10.1055/s-2007-994012

[38] Lominadze, D., *et al.* (2010) Mechanisms of Fibrinogen-Induced Microvascular Dysfunction during Cardiovascular Disease. *Acta Physiologica* (*Oxf*), **198**, 1-13. https://doi.org/10.1111/j.1748-1716.2009.02037.x

[39] Lominadze, D., *et al.* (2005) Fibrinogen and Fragment D-Induced Vascular Constriction. *American Journal of Physiology-Heart and Circulatory Physiology*, **288**, H1257-H1264. https://doi.org/10.1152/ajpheart.00856.2004

[40] Muradashvili, N., *et al.* (2011) Fibrinogen Alters Mouse Brain Endothelial Cell Layer Integrity Affecting Vascular Endothelial Cadherin. *Biochemical and Biophysical Research Communications*, **413**, 509-514. https://doi.org/10.1016/j.bbrc.2011.07.133

[41] Patibandla, P.K., *et al.* (2009) Fibrinogen Induces Alterations of Endothelial Cell Tight Junction Proteins. *Journal of Cellular Physiology*, **221**, 195-203. https://doi.org/10.1002/jcp.21845

[42] Tarkowski, E., *et al.* (2003) Correlation between Intrathecal Sulfatide and TNF-Alpha Levels in Patients with Vascular Dementia. *Dementia and Geriatric Cognitive Disorders*, **15**, 207-211. https://doi.org/10.1159/000068780

[43] Guldiken, B., *et al.* (2007) Serum Osteoprotegerin Levels in Patients with Acute Atherothrombotic Stroke and Lacunar Infarct. *Thrombosis Research*, **120**, 511-516. https://doi.org/10.1016/j.thromres.2006.12.004

[44] Schoch, H.J., Fischer, S. and Marti, H.H. (2002) Hypoxia-Induced Vascular Endothelial Growth Factor Expression Causes Vascular Leakage in the Brain. *Brain*, **125**, 2549-2557. https://doi.org/10.1093/brain/awf257

[45] Zhang, J.B., *et al.* (2016) Association of Serum Vascular Endothelial Growth Factor Levels and Cerebral Microbleeds in Patients with Alzheimer's Disease. *European Journal of Neurology*, **23**, 1337-1342. https://doi.org/10.1111/ene.13030

[46] Perkins, L.A., Anderson, C.J. and Novelli, E.M. (2019) Targeting P-Selectin Adhesion Molecule in Molecular Imaging: P-Selectin Expression as a Valuable Imaging Biomarker of Inflammation in Cardiovascular Disease. *Journal of Nuclear Medicine*, **60**, 1691-1697. https://doi.org/10.2967/jnumed.118.225169

[47] De Leeuw, F.E., *et al.* (2002) Endothelial Cell Activation Is Associated with Cerebral White Matter Lesions in Patients with Cerebrovascular Disease. *Annals of the New York Academy of Sciences*, **977**, 306-314. https://doi.org/10.1111/j.1749-6632.2002.tb04831.x

[48] Fassbender, K., *et al.* (1999) Adhesion Molecules in Cerebrovascular Diseases. Evidence for an Inflammatory Endothelial Activation in Cerebral Large- and Small-Vessel Disease. *Stroke*, **30**, 1647-1650. https://doi.org/10.1161/01.STR.30.8.1647

[49] Kario, K., *et al.* (2001) Hyperinsulinemia and Hemostatic Abnormalities Are Associated with Silent Lacunar Cerebral Infarcts in Elderly Hypertensive Subjects. *Journal of the American College of Cardiology*, **37**, 871-877. https://doi.org/10.1016/S0735-1097(00)01172-4

[50] Low, A., *et al.* (2019) Inflammation and Cerebral Small Vessel Disease: A Systematic Review. *Ageing Research Reviews*, **53**, Article 100916. https://doi.org/10.1016/j.arr.2019.100916

[51] Wada, M., *et al.* (2011) Plasma Fibrinogen, Global Cognitive Function, and Cerebral Small Vessel Disease: Results of a Cross-Sectional Study in Community-Dwelling Japanese Elderly. *Internal Medicine*, **50**, 999-1007. https://doi.org/10.2169/internalmedicine.50.4752

[52] Fornage, M., *et al.* (2008) Biomarkers of Inflammation and MRI-Defined Small Vessel Disease of the Brain: The Cardiovascular Health Study. *Stroke*, **39**, 1952-1959. https://doi.org/10.1161/STROKEAHA.107.508135

[53] Mitaki, S., *et al.* (2016) C-Reactive Protein Levels Are Associated with Cerebral Small Vessel-Related Lesions. *Acta Neurologica Scandinavica*, **133**, 68-74. https://doi.org/10.1111/ane.12440

[54] Hilal, S., *et al.* (2018) C-Reactive Protein, Plasma Amyloid-β Levels, and Their Interaction with Magnetic Resonance Imaging Markers. *Stroke*, **49**, 2692-2698. https://doi.org/10.1161/STROKEAHA.118.022317

[55] Koh, S.H., *et al.* (2011) Microbleeds and Free Active MMP-9 Are Independent Risk Factors for Neurological Deterioration in Acute Lacunar Stroke. *European Journal of Neurology*, **18**, 158-164. https://doi.org/10.1111/j.1468-1331.2010.03100.x

[56] Noz, M.P., *et al.* (2018) Trained Immunity Characteristics Are Associated with Progressive Cerebral Small Vessel Disease. *Stroke*, **49**, 2910-2917. https://doi.org/10.1161/STROKEAHA.118.023192

[57] Vermeer, S.E., *et al.* (2002) Homocysteine, Silent Brain Infarcts, and White Matter Lesions: The Rotterdam Scan Study. *Annals of Neurology*, **51**, 285-289. https://doi.org/10.1002/ana.10111

[58] Pavlovic, A.M., *et al.* (2011) Increased Total Homocysteine Level Is Associated with Clinical Status and Severity of White Matter Changes in Symptomatic Patients with Subcortical Small Vessel Disease. *Clinical Neurology and Neurosurgery*, **113**, 711-715. https://doi.org/10.1016/j.clineuro.2011.07.004

[59] Gao, Y., *et al.* (2015) Homocysteine Level Is Associated with White Matter Hyperintensity Locations in Patients with Acute Ischemic Stroke. *PLOS ONE*, **10**, e0144431. https://doi.org/10.1371/journal.pone.0144431

[60] Altendahl, M., *et al.* (2020) An IL-18-Centered Inflammatory Network as a Biomarker for Cerebral White Matter Injury. *PLOS ONE*, **15**, e0227835. https://doi.org/10.1371/journal.pone.0227835