Advances in Clinical Medicine 临床医学进展, 2024, 14(12), 551-556
Published Online December 2024 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2024.14123116

Hans汉斯

脑白质高信号与缺血性脑卒中关系的研究进展

董　昱，刘　敏，朱　珠

西安医学院研究生处，陕西　西安

收稿日期：2024年11月16日；录用日期：2024年12月9日；发布日期：2024年12月17日

摘　要

随着全球人口老龄化的加速，健康老龄化的重要性愈发凸显。脑白质高信号在老年人群中普遍存在，作为脑小血管病的重要影像学表现，它通常被视为大脑和心血管健康状况不佳的标志。已有研究表明，脑白质高信号与脑卒中之间存在显著关联。脑卒中是全球第二大死亡原因，其中最常见的是缺血性脑卒中，因其高致残率，严重影响患者的身心健康和生活质量。因此，深入理解脑白质高信号与缺血性脑卒中之间的关系显得尤为重要。本文将从脑白质高信号的病因机制、评估方法以及其与缺血性脑卒中发生风险和预后结局等方面进行综述，旨在为脑白质高信号的相关机制研究提供参考，并为深入探讨其与缺血性脑卒中的相关性提供依据。

关键词

脑白质高信号，缺血性脑卒中，预后，机制

Research Progress on the Relationship between White Matter Hyperintensity and Ischemic Stroke

Yu Dong, Min Liu, Zhu Zhu

Graduate School of Xi'an Medical College, Xi'an Shaanxi

Received: Nov. 16th, 2024; accepted: Dec. 9th, 2024; published: Dec. 17th, 2024

Abstract

With the accelerating aging of the global population, the importance of healthy aging is becoming

文章引用: 董昱, 刘敏, 朱珠. 脑白质高信号与缺血性脑卒中关系的研究进展[J]. 临床医学进展, 2024, 14(12): 551-556.
DOI: 10.12677/acm.2024.14123116

increasingly prominent. White matter hyperintensity is commonly observed in the elderly and is considered a significant imaging manifestation of cerebral small vessel disease. It is often regarded as a marker of poor brain and cardiovascular health. Existing studies have indicated a significant association between white matter hyperintensity and stroke. Stroke is the second leading cause of death worldwide, with ischemic stroke being the most common type. Due to its high rates of disability, ischemic stroke severely impacts patients' physical and mental health, as well as their quality of life. Therefore, it is crucial to gain a deeper understanding of the relationship between white matter hyperintensity and ischemic stroke. This paper reviews the etiology and mechanisms of white matter hyperintensity, assessment methods, and its association with the risk of ischemic stroke and prognostic outcomes. The aim is to provide references for the mechanism of white matter hyperintensity and to substantiate further exploration of its correlation with ischemic stroke.

Keywords

White Matter Hyperintensity, Ischemic Stroke, Prognosis, Mechanisms

1. 引言

脑白质高信号(white matter hyperintensity, WMH)是大脑白质中的点状、斑片状或融合性病变，该病变在磁共振成像(magnetic resonance imaging, MRI)的 T2 加权像(T2 weighted imaging, T2WI)和液体衰减反转恢复序列(fluid-attenuated inversion recovery, FLAIR)中呈高信号，在 T1 加权像(T1 weighted imaging, T1WI)中呈等或低信号[1]。WMH 是脑小血管疾病(cerebral small vessel disease, CSVD)的重要影像特征，可反映脑微血管功能[2]。近年来，随着世界人口老龄化的加速和影像技术的发展，WMH 的发生率和检出率显著升高[3]。多项研究表明 WMH 与缺血性脑卒中(ischemic stroke, IS)的发生和预后密切相关[4]-[6]。IS 是一种常见的脑卒中类型，据统计 IS 占所有新发卒中的 65.3%，已成为威胁公众健康的重要问题[7]-[9]。然而，目前医学界对于 WMH 与 IS 发生风险及其预后作用的了解仍然十分有限。因此，有关 WMH 与 IS 的研究仍是神经病学研究领域的一项热点。本文就 WMH 的病因机制及其与 IS 的关系进行综述，以期为 WMH 和 IS 的深入研究提供依据，并为临床采取针对性防治措施提供参考。

2. 脑白质高信号的病因机制

WMH 最早于 1986 年由加拿大神经病学专家 Hachinski 等人提出[10]。WMH 在中老年人群中普遍存在，其患病率随着年龄的增加，呈现出逐年上涨的趋势[11] [12]。近期大量研究表明，WMH 是大脑和心血管健康状况不佳的标志，预示着中风、认知能力下降、抑郁和死亡的风险增加[13]。然而，其发病机制目前临床上学说众多，我们将从以下的 3 个主要学说展开探讨。

2.1. 脑灌注学说

脑白质的血液供应主要依赖于两部分血管系统：一是源自大脑表面软脑膜血管网的长穿支动脉；二是来自室管膜下动脉的脉络膜动脉或纹状体动脉的终末分支。由于上述两部分血管之间的吻合稀少甚至缺乏，使得脑室周围的脑白质处于动脉交界区，也就是所谓的“分水岭区”。因此，当脑血流量减少时，该区域极易受到损伤[14]。临床上 WMH 与脑血流灌注的研究较多，多项研究表明 WMH 患者的静息脑

血流量低于无 WMH 的患者[15]。一项基于小卒中/短暂性脑缺血发作患者的纵向队列研究表明，基线脑血流量每分钟每增加 1 mL/100g，随访成像中新出现 WMH 的几率会降低 0.61，脑血流量低的白质区域在后续的随访成像中可产生新的 WMH [16]。多项大型纵向研究表明，WMH 严重程度和脑血流量负相关[2]。上述研究均表明脑灌注不足可能是 WMH 发生和发展的一个重要机制。

2.2. 血脑屏障学说

血脑屏障由血管内皮细胞之间的紧密连接、基底膜、周细胞、神经元及星形胶质细胞的突触末端共同组成。这一生理结构能够有效保护脑组织免受外周血液中有害物质侵害，维持脑组织内环境的稳定[17]。根据 Farrall 等进行的一项荟萃分析可知，随着 WMH 负荷的增加，血脑屏障的通透性也显著增加[18]。一项基于动态对比增强磁共振成像技术的观察性研究表明，血脑屏障渗漏量与 WMH 体积正相关，与信息处理速度负相关，进一步证明了 WMH 区域血脑屏障通透性增加，脑组织内环境稳定性被打破，进而损害大脑神经纤维[19]。因此，血脑屏障功能障碍是 WMH 发生和发展的一个重要原因。

2.3. 基因遗传学说

近年来，WMH 病因机制的研究逐渐聚焦于基因遗传因素，且有研究表明，遗传因素在 WMH 发展中可能发挥高达 55%~80%的重要作用[20]。多位研究者通过全基因组连锁分析发现，WMH 与 1 号、4 号、5 号和 11 号染色体存在关联[3]。Fernandez 等研究发现，有 7 个基因与 WMH 相关，包括 *MMP*13、*PON*1、*NOS*3、*IL5RA*、*A2M*、*ITGB*6 和 *IL5RA* [21]。然而，目前 WMH 的确切基因位点尚不明确，未来还需进一步研究。

3. 脑白质高信号的评估方式

目前，WMH 的评估方式较多，包括多种半自动化和自动化评估法，但由于部分评估方式尚未成熟，且其再现性和可比性缺乏深入表征，故国际脑小血管病影像诊断标准(STRIVE-1)和欧盟神经退行性疾病联合组织(HARNESS)均指出：评估 WMH 可使用经过充分验证的视觉评分[22]。其中，临床上最常见的视觉评分为 Fazekas 评分。Fazekas 评分是基于头颅 MRI-T2WI 或 FLAIR 序列图像分别对脑室旁白质高信号(PVWM)和深部白质高信号(DWM)进行评分，PVWM 评分为：无(0 分)，帽状/铅笔样薄层(1 分)，光滑的晕圈状(2 分)，不规则且延伸到深部白质(3 分)；DWM 评分为：无(0 分)，点状(1 分)，开始融合(2 分)，大面积融合(3 分)；两者相加即为总分，总分 <3 分为轻度，≥ 3 分为中重度[23]。

4. 脑白质高信号与缺血性脑卒中

随着现代科学技术的不断发展和人口老龄化的加剧，WMH 与 IS 之间关系的研究日益增多，WMH 对 IS 的影响几乎贯穿其三级预防的全过程。

4.1. 脑白质高信号与缺血性脑卒中的发生风险

目前，多项基于人口的前瞻性研究均表明，WMH 严重程度与首次卒中风险，卒中复发风险及总死亡率有关[5] [24]-[26]。Kuller 等通过对 3293 名心血管健康的社区人员进行颅脑 MRI 检查和 7 年随访，研究结果表明，随着 WMH 严重程度的增加，中风的相对风险显着增加，严重的 WMH 参与者中风风险为每年 2.8%，而轻度 WMH 参与者的中风风险仅为 0.6% [26]。一项基于 9522 名脑卒中患者的队列研究表明，WMH 与卒中后 5 年内的复发性卒中有关，与轻度/中度 WMH 相比，重度 WMH 参与者的卒中复发率显著更高[27]。一项纳入 16,000 多名参与者的系统评价和荟萃分析表明，WMH 与脑卒中和死亡风险的增加有关[4]。因此，WMH 是脑卒中事件发生风险的重要危险因素，早期评估与控制可能会有效预防

脑卒中的发生风险。

4.2. 脑白质高信号与缺血性脑卒中的预后结局

目前，多数研究表明，WMH 严重程度与 IS 急性期患者再灌注治疗预后相关。一项队列研究表明，重度 WMH 与接受静脉组织纤溶酶原激活剂的急性 IS 患者术后 3 个月不良功能结局独立相关，提示重度 WMH 与脑卒中后功能结局不佳有关[28]。Kongbunkiat 等进行的荟萃分析纳入了已发表的 15 项关于接受静脉或动脉内溶栓治疗的急性 IS 患者的研究，结果表明 WMH 的存在和严重程度始终与症状性脑出血风险增加和溶栓后不良功能结局相关[29]。一项前瞻性多中心研究表明，中度至重度 WMH 与接受血管内治疗的 IS 患者预后较差相关[30]。此外，一项纳入 7 项队列研究，涉及 1294 名参与者的荟萃分析表明，伴有重度 WMH 的 IS 机械取栓患者预后较差[31]。近期，一项基于深度学习的研究表明，重度 WMH 与急性 IS 静脉溶栓治疗后症状性脑出血显著相关[32]。因此，IS 无论是溶栓治疗还是机械取栓治疗，患者预后与 WMH 严重程度之间的关系均十分密切。

然而，仍有部分证据表明，WMH 严重程度与 IS 急性期患者再灌注治疗预后不良无显著相关性。Mcalpine 等研究表明，WMH 的严重程度与接受静脉溶栓治疗后的 IS 患者早期神经功能恢复之间关联性无法被证明[33]。一项纳入 293 例接受机械血栓切除术的急性 IS 患者的回顾性研究表明，WMH 严重程度与参与者术后 3 个月不良预后及脑实质出血均无明显相关性[34]。Atchaneeyasakul 等的研究也同样表明，WMH 负荷与接受机械血栓切除术的急性 IS 患者术后不良预后无显著相关[35]。因此，WMH 严重程度是否影响接受再灌注治疗的急性 IS 患者预后效果目前尚无定论。

5. 总结与展望

大脑健康是健康老龄化的核心内容，由于中老年人群中 WMH 普遍存在，所以关于 WMH 病因机制及临床危害性的相关研究日益增多[36]。现阶段关于其病因机制的研究中，脑灌注学说为目前临床上较为认可的学说，而上述提到的血脑屏障和基因遗传学说尚需更多的证据支持。未来可根据 WMH 的不同病因机制细化 WMH 分型，确定衍生表型的全新治疗靶点，以期延缓甚至逆转 WMH 的发展。有关 WMH 可增加 IS 发生风险的结论已较为明确，未来可依托神经影像与大数据科学的发展，进一步细化脑白质病变分区和提高 WMH 早期检出率，为 IS 的早期预防提供机会。关于 WMH 严重程度是否影响 IS 患者再灌注治疗预后尚不明确。目前，此类的相关研究多局限于回顾性、单中心和小样本设计，此外，各个研究方案之间尚无统一的研究标准，使得结论难以确定。因此，未来需统一相关研究标准，采用大样本、前瞻性、多中心研究进一步论证，旨在为提高 IS 再灌注治疗患者生存质量提供契机。

参考文献

[1] Wardlaw, J.M., Smith, E.E., Biessels, G.J., Cordonnier, C., Fazekas, F., Frayne, R., *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

[2] Wardlaw, J.M., Smith, C. and Dichgans, M. (2019) Small Vessel Disease: Mechanisms and Clinical Implications. *The Lancet Neurology*, **18**, 684-696. https://doi.org/10.1016/s1474-4422(19)30079-1

[3] 马艳婷, 李云霞, 刘梦, 等. 脑白质高信号发生机制及其与临床症状相关性研究进展[J]. 陕西医学杂志, 2022, 51(6): 767-769.

[4] Debette, S., Schilling, S., Duperron, M., Larsson, S.C. and Markus, H.S. (2019) Clinical Significance of Magnetic Resonance Imaging Markers of Vascular Brain Injury: A Systematic Review and Meta-Analysis. *JAMA Neurology*, **76**, 81-94. https://doi.org/10.1001/jamaneurol.2018.3122

[5] Debette, S., Beiser, A., DeCarli, C., Au, R., Himali, J.J., Kelly-Hayes, M., *et al*. (2010) Association of MRI Markers of Vascular Brain Injury with Incident Stroke, Mild Cognitive Impairment, Dementia, and Mortality: The Framingham Offspring Study. *Stroke*, **41**, 600-606. https://doi.org/10.1161/strokeaha.109.570044

[6] 刘丹, 钟镝, 李国忠. 脑白质高信号对急性缺血性卒中患者功能恢复的影响的研究进展[J]. 中国卒中杂志, 2017, 12(8): 753-758.

[7] GBD 2019 Stroke Collaborators (2021) Global, Regional, and National Burden of Stroke and Its Risk Factors, 1990-2019: A Systematic Analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*, **20**, 795-820. https://doi.org/10.1016/S1474-4422(21)00252-0

[8] Xie, H., Gao, M., Lin, Y., Yi, Y. and Liu, Y. (2022) An Emergency Nursing and Monitoring Procedure on Cognitive Impairment and Neurological Function Recovery in Patients with Acute Cerebral Infarction. *NeuroRehabilitation*, **51**, 161-170. https://doi.org/10.3233/nre-210310

[9] GBD 2021 Stroke Risk Factor Collaborators (2024) Global, Regional, and National Burden of Stroke and Its Risk Factors, 1990-2021: A Systematic Analysis for the Global Burden of Disease Study 2021. *Lancet Neurol*, **23**, 973-1003. https://doi.org/10.1016/S1474-4422(24)00369-7

[10] Hachinski, V.C., Potter, P. and Merskey, H. (1986) Leuko-Araiosis: An Ancient Term for a New Problem. *Canadian Journal of Neurological Sciences/Journal Canadien des Sciences Neurologiques*, **13**, 533-534. https://doi.org/10.1017/s0317167100037264

[11] Wen, W., Sachdev, P.S., Li, J.J., Chen, X. and Anstey, K.J. (2008) White Matter Hyperintensities in the Forties: Their Prevalence and Topography in an Epidemiological Sample Aged 44-48. *Human Brain Mapping*, **30**, 1155-1167. https://doi.org/10.1002/hbm.20586

[12] de Leeuw, F. (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 & Psychiatry*, **70**, 9-14. https://doi.org/10.1136/jnnp.70.1.9

[13] Ottavi, T.P., Pepper, E., Bateman, G., Fiorentino, M. and Brodtmann, A. (2023) Consensus Statement for the Management of Incidentally Found Brain White Matter Hyperintensities in General Medical Practice. *Medical Journal of Australia*, **219**, 278-284. https://doi.org/10.5694/mja2.52079

[14] 蔡文捷, 郁金泰. 脑白质高信号与认知功能关系的研究进展[J]. 中国医学前沿杂志(电子版), 2020, 12(10): 18-22.

[15] Shi, Y., Thrippleton, M.J., Makin, S.D., Marshall, I., Geerlings, M.I., de Craen, A.J., *et al*. (2016) Cerebral Blood Flow in Small Vessel Disease: A Systematic Review and Meta-Analysis. *Journal of Cerebral Blood Flow & Metabolism*, **36**, 1653-1667. https://doi.org/10.1177/0271678x16662891

[16] Bernbaum, M., Menon, B.K., Fick, G., Smith, E.E., Goyal, M., Frayne, R., *et al*. (2015) Reduced Blood Flow in Normal White Matter Predicts Development of Leukoaraiosis. *Journal of Cerebral Blood Flow & Metabolism*, **35**, 1610-1615. https://doi.org/10.1038/jcbfm.2015.92

[17] Shen, J., Xu, G., Zhu, R., Yuan, J., Ishii, Y., Hamashima, T., *et al*. (2018) PDGFR-β Restores Blood-Brain Barrier Functions in a Mouse Model of Focal Cerebral Ischemia. *Journal of Cerebral Blood Flow & Metabolism*, **39**, 1501-1515. https://doi.org/10.1177/0271678x18769515

[18] Farrall, A.J. and Wardlaw, J.M. (2009) Blood-Brain Barrier: Ageing and Microvascular Disease—Systematic Review and Meta-Analysis. *Neurobiology of Aging*, **30**, 337-352. https://doi.org/10.1016/j.neurobiolaging.2007.07.015

[19] Freeze, W.M., Jacobs, H.I.L., de Jong, J.J., Verheggen, I.C.M., Gronenschild, E.H.B.M., Palm, W.M., *et al*. (2020) White Matter Hyperintensities Mediate the Association between Blood-Brain Barrier Leakage and Information Processing Speed. *Neurobiology of Aging*, **85**, 113-122. https://doi.org/10.1016/j.neurobiolaging.2019.09.017

[20] Sun, L., Hui, L., Li, Y., Chen, X., Liu, R. and Ma, J. (2022) Pathogenesis and Research Progress in Leukoaraiosis. *Frontiers in Human Neuroscience*, **16**, Article 902731. https://doi.org/10.3389/fnhum.2022.902731

[21] Fernandez-Cadenas, I., Mendioroz, M., Domingues-Montanari, S., Del Rio-Espinola, A., Delgado, P., Ruiz, A., *et al*. (2010) Leukoaraiosis Is Associated with Genes Regulating Blood-Brain Barrier Homeostasis in Ischaemic Stroke Patients. *European Journal of Neurology*, **18**, 826-835. https://doi.org/10.1111/j.1468-1331.2010.03243.x

[22] Duering, M., Biessels, G.J., Brodtmann, A., Chen, C., Cordonnier, C., de Leeuw, F., *et al*. (2023) Neuroimaging Standards for Research into Small Vessel Disease—Advances since 2013. *The Lancet Neurology*, **22**, 602-618. https://doi.org/10.1016/s1474-4422(23)00131-x

[23] Fazekas, F., Chawluk, J., Alavi, A., Hurtig, H. and Zimmerman, R. (1987) MR Signal Abnormalities at 1.5 T in Alzheimer's Dementia and Normal Aging. *American Journal of Roentgenology*, **149**, 351-356. https://doi.org/10.2214/ajr.149.2.351

[24] Bokura, H., Kobayashi, S., Yamaguchi, S., Iijima, K., Nagai, A., Toyoda, G., *et al*. (2006) Silent Brain Infarction and Subcortical White Matter Lesions Increase the Risk of Stroke and Mortality: A Prospective Cohort Study. *Journal of Stroke and Cerebrovascular Diseases*, **15**, 57-63. https://doi.org/10.1016/j.jstrokecerebrovasdis.2005.11.001

[25] Debette, S. and Markus, H.S. (2010) The Clinical Importance of White Matter Hyperintensities on Brain Magnetic Resonance Imaging: Systematic Review and Meta-Analysis. *BMJ*, **341**, c3666-c3666. https://doi.org/10.1136/bmj.c3666

[26] Kuller, L.H., Longstreth, W.T., Arnold, A.M., Bernick, C., Bryan, R.N. and Beauchamp, N.J. (2004) White Matter Hyperintensity on Cranial Magnetic Resonance Imaging: A Predictor of Stroke. *Stroke*, **35**, 1821-1825. https://doi.org/10.1161/01.str.0000132193.35955.69

[27] Kumral, E., Güllüoğlu, H., Alakbarova, N., Karaman, B., Deveci, E.E., Bayramov, A., *et al*. (2015) Association of Leukoaraiosis with Stroke Recurrence within 5 Years after Initial Stroke. *Journal of Stroke and Cerebrovascular Diseases*, **24**, 573-582. https://doi.org/10.1016/j.jstrokecerebrovasdis.2014.10.002

[28] Yang, C., Hung, C., Su, H., Lin, H., Chen, C., Lin, C., *et al*. (2018) Leukoaraiosis and Risk of Intracranial Hemorrhage and Outcome after Stroke Thrombolysis. *PLOS ONE*, **13**, e0196505. https://doi.org/10.1371/journal.pone.0196505

[29] Kongbunkiat, K., Wilson, D., Kasemsap, N., Tiamkao, S., Jichi, F., Palumbo, V., *et al*. (2017) Leukoaraiosis, Intracerebral Hemorrhage, and Functional Outcome after Acute Stroke Thrombolysis. *Neurology*, **88**, 638-645. https://doi.org/10.1212/wnl.0000000000003605

[30] Mistry, E.A., Mistry, A.M., Mehta, T., Arora, N., Starosciak, A.K., La Rosa, F.D.L.R., *et al*. (2020) White Matter Disease and Outcomes of Mechanical Thrombectomy for Acute Ischemic Stroke. *American Journal of Neuroradiology*, **41**, 639-644. https://doi.org/10.3174/ajnr.a6478

[31] Huo, L., Chen, P., Wang, Z., Li, X., Zhou, J., Wang, C., *et al*. (2020) Impact of Leukoaraiosis Severity on the Association of Outcomes of Mechanical Thrombectomy for Acute Ischemic Stroke: A Systematic Review and a Meta-Analysis. *Journal of Neurology*, **268**, 4108-4116. https://doi.org/10.1007/s00415-020-10167-0

[32] van Voorst, H., Pitkänen, J., van Poppel, L., de Vries, L., Mojtahedi, M., Martou, L., *et al*. (2024) Deep Learning-Based White Matter Lesion Volume on CT Is Associated with Outcome after Acute Ischemic Stroke. *European Radiology*, **34**, 5080-5093. https://doi.org/10.1007/s00330-024-10584-z

[33] McAlpine, H., Churilov, L., Mitchell, P., Dowling, R., Teo, S. and Yan, B. (2014) Leukoaraiosis and Early Neurological Recovery after Intravenous Thrombolysis. *Journal of Stroke and Cerebrovascular Diseases*, **23**, 2431-2436. https://doi.org/10.1016/j.jstrokecerebrovasdis.2014.05.012

[34] Mechtouff, L., Nighoghossian, N., Amaz, C., Buisson, M., Berthezène, Y., Derex, L., *et al*. (2019) White Matter Burden Does Not Influence the Outcome of Mechanical Thrombectomy. *Journal of Neurology*, **267**, 618-624. https://doi.org/10.1007/s00415-019-09624-2

[35] Atchaneeyasakul, K., Leslie-Mazwi, T., Donahue, K., Giese, A. and Rost, N.S. (2017) White Matter Hyperintensity Volume and Outcome of Mechanical Thrombectomy with Stentriever in Acute Ischemic Stroke. *Stroke*, **48**, 2892-2894. https://doi.org/10.1161/strokeaha.117.018653

[36] de Havenon, A., Smith, E.E., Sharma, R., Falcone, G.J., Bangad, A., Prabhakaran, S., *et al*. (2023) Improvement in the Prediction of Cerebrovascular Events with White Matter Hyperintensity. *Journal of the American Heart Association*, **12**, e029374. https://doi.org/10.1161/jaha.123.029374