

血管源性脑白质高信号与血管性认知障碍的相关性研究

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摘要

目的: 探讨血管源性脑白质高信号(WMH)的严重程度与血管性认知障碍(VCI)相关性, 并分析其对不同认知功能的影响。方法: 本研究共纳入102例WMH患者, 根据临床及神经心理学测验等结果综合评估, 将患者分为血管性认知障碍组(VCI组, $n = 45$)与非认知障碍组(非VCI组, $n = 57$)。收集所有患者的基线资料、实验室指标和影像学检查, 采用Fazekas量表评估WMH严重程度, 使用简易精神状态量表(MMSE)及血管性痴呆评估量表(VaDAS-cog)评估认知功能。通过单因素及多因素Logistic回归分析WMH与VCI的相关性。通过ROC曲线评估预测效能。应用Spearman相关与多元线性回归分析WMH严重程度与各认知评分的相关性。结果: VCI组患者年龄、文化程度、脑梗死病史、抗栓药物的使用、他汀类药物的使用、白细胞计数、纤维蛋白原、Fazekas评分、MMSE评分、VaDAS-cog总分及其各子项评分与非VCI组比较, 差异均有统计学意义($P < 0.05$)。在调整了年龄、文化程度、脑梗死病史、白细胞计数及纤维蛋白原等混杂因素后, 多因素Logistic回归显示WMH Fazekas评分仍是VCI的独立危险因素($OR = 1.936$, 95%CI: 1.245~3.012, $P = 0.003$)。ROC曲线分析显示, 联合模型的预测效能最高, 其AUC为0.892, 敏感度为93.3%, 特异度为63.2%。在校正上述混杂因素的线性模型中, WMH Fazekas评分与MMSE评分($\beta = -0.207$, $P = 0.005$)呈独立负相关, 与VaDAS-cog总分($\beta = 0.236$, $P = 0.001$)及各子项评分($P < 0.05$)呈独立正相关, 其中WMH对执行/注意功能($\beta = 0.254$, $P = 0.003$)效应较为突出。结论: 脑白质高信号是血管性认知障碍的独立危险因素, 其中执行/注意功能为主要受累的认知领域。

关键词

脑白质高信号, 血管性痴呆评估量表, 血管性认知障碍

Correlation Study between White Matter Hyperintensities and Vascular Cognitive Impairment

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Abstract

Objective: To investigate the correlation between the severity of vascular white matter hyperintensities (WMH) and vascular cognitive impairment (VCI), and to analyze its impact on different cognitive domains. **Methods:** A total of 102 patients with WMH were enrolled in this study. Based on comprehensive clinical and neuropsychological assessments, patients were divided into a vascular cognitive impairment group (VCI group, $n = 45$) and a non-cognitive impairment group (Non-VCI group, $n = 57$). Baseline characteristics, laboratory parameters, and neuroimaging data were collected for all patients. WMH severity was assessed using the Fazekas scale. Cognitive function was evaluated using the Mini-Mental State Examination (MMSE) and the Vascular Dementia Assessment Scale-cognitive subscale (VaDAS-cog). Univariate and multivariate logistic regression analyses were employed to examine the association between WMH and VCI. The predictive value was assessed using receiver operating characteristic (ROC) curve analysis. Spearman's correlation and multiple linear regression were applied to analyze the relationship between WMH severity and various cognitive scores. **Results:** Compared to the Non-VCI group, the VCI group showed significant differences in age, education level, history of cerebral infarction, use of antithrombotic drugs, use of statins, white blood cell count, fibrinogen level, Fazekas score, MMSE score, VaDAS-cog total score, and all its subdomain scores ($P < 0.05$). After adjusting for confounding factors including age, education level, history of cerebral infarction, white blood cell count, and fibrinogen, multivariate logistic regression revealed that a higher Fazekas score remained an independent risk factor for VCI (OR = 1.963, 95% CI: 1.245~3.012, $P = 0.003$). ROC curve analysis indicated that the combined predictive model had the highest efficacy, with an area under the curve (AUC) of 0.892, a sensitivity of 93.3%, and a specificity of 63.2%. In linear regression models adjusted for the aforementioned confounders, the Fazekas score was independently and negatively correlated with the MMSE score ($\beta = -0.207$, $P = 0.005$), and independently and positively correlated with the VaDAS-cog total score ($\beta = 0.236$, $P = 0.001$) and all its subdomain scores ($P < 0.05$). Notably, the association between WMH and the executive/attention function domain was particularly prominent ($\beta = 0.254$, $P = 0.003$). **Conclusion:** White matter hyperintensities constitute an independent risk factor for vascular cognitive impairment, with the executive/attention domain being the primarily affected cognitive sphere.

Keywords

White Matter Hyperintensities, Vascular Dementia Assessment Scale-Cognitive Subscale, Vascular Cognitive Impairment

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1. 引言

推测为血管源性的脑白质高信号(white matter hyperintensity, WMH)定义为脑白质内形状不一、大小不等的异常信号区域,是脑小血管病在磁共振成像上的核心影像学标志之一[1]。随着人口老龄化进程加

速,WMH 在老年人群中的检出率显著升高,已成为一个重要的公共健康问题[2]。血管性认知障碍(vascular cognitive impairment, VCI)是指由脑血管病变及其危险因素导致的一系列从轻度认知损害到痴呆的临床综合征,是我国老年人认知障碍的常见原因[3]。脑小血管病被认为是引起 VCI 的最主要血管性病因,其中,皮质下缺血性血管性认知障碍以 WMH 和腔隙灶为其特征性影像学改变[4]。近年来,越来越多的证据表明,WMH 并非良性的影像学表现,而是与认知功能下降密切相关。多项研究结果已证实,WMH 的存在及其严重程度是整体认知功能衰退和注意力、执行功能和记忆力等特定认知领域损害的独立预测因子[5]-[7]。WMH 对认知功能的影响可能因其位置、体积及严重程度的不同而有所差异[8]。一项前瞻性队列研究表明,在基线认知正常的脑小血管病患者中,脑白质高信号的严重程度是预测血管性认知障碍发生的独立影像学标志物之一[9]。本次研究使用 Fazekas 量表评估 WMH,与血管性认知障碍进行相关性分析,并探讨其认知功能的影响。

2. 资料与方法

2.1. 一般资料

选取 2025 年 3 月至 2025 年 10 月于安徽医科大学第四附属医院神经内科住院的 102 例血管源性脑白质高信号患者为研究对象。纳入标准:经头颅 MRI 证实存在脑白质高信号;年龄 ≥ 45 岁;能配合神经心理学测试。排除标准:患有其他可能导致认知障碍的神经系统疾病,如阿尔茨海默病、帕金森病、脑肿瘤、正常颅压脑积水等;患有严重的精神疾病;存在 MRI 检查禁忌,不能完成 MRI 检查;合并严重肝、肾功能不全或其他系统性疾病终末期。本研究经医院伦理委员会批准,所有患者或其家属均签署知情同意书。

2.2. 研究方法

2.2.1. 临床资料收集

记录所有患者的年龄、性别、文化程度、脑梗死病史、抗栓药使用情况、他汀类药物使用情况、高血压病史、糖尿病病史、白细胞计数、纤维蛋白原、低密度脂蛋白、同型半胱氨酸及磁共振影像学结果。

2.2.2. 血管性认知障碍的诊断

依据 2024 年中国血管性认知障碍诊治指南,诊断需具备 3 个要素:(1)神经心理评估或主诉存在至少一个认知域受损;(2)存在血管危险因素、脑血管病史或影像学显示的脑血管病变等血管性脑损伤证据;(3)明确血管性脑损害在认知损害中占主导地位[3]。

2.2.3. WMH 的诊断

诊断标准:双侧大脑白质内点、片、融合状或对称分布的 T1WI 等或低信号(不如脑脊液信号低),T2WI、T2FLAIR 及质子像高信号[10]。严重程度的诊断基于 Fazekas 视觉直观评分量表,该量表在轴位 FLAIR 序列上对脑室周围白质和深部白质两个区域分别进行评分:脑室周围区域,0 分为无病变,1 分为帽状或铅笔样薄层病变,2 分为光滑的晕圈状病变,3 分为不规则高信号并延伸至深部白质;深部白质区域,0 分为无病变,1 分为点状病灶,2 分为病灶开始融合,3 分为大面积融合的病灶。本研究将上述两个区域的评分相加得到总分(范围 0~6 分)[11]。

2.2.4. 认知功能评估

采用简易精神状态检查表(MMSE)评估总体认知功能,总分 30 分,其分界值与受教育程度有关,文盲者 ≤ 17 分,小学文化者 ≤ 20 分、中学或以上文化者 ≤ 24 分为认知功能障碍。采用血管性痴呆评估量表-认知部分(VaDAS-cog)评估记忆力、定向力、语言、运用、执行/注意功能等特定认知域功能,得分越高表

示认知障碍越严重,与过去沿用的血管性痴呆评定量表 ADAS-cog 相比,VaDAS-cog 增加了语言流畅性、数字划消试验和迷宫试验等,侧重注意/执行功能的检测,对脑白质病变的严重度具有更好的判断能力[12]-[14]。

2.2.5. 精神行为评估

采用神经精神症状问卷(neuropsychiatric inventory, NPI)评估精神行为症状[3],包括妄想、幻觉、激越/攻击行为、抑郁/心境不悦、焦虑、欣快、淡漠、行为失控、易怒/情绪不稳、异常举动、夜间行为以及食欲/饮食变更等,由熟悉患者的照料者对每个症状的频率和严重程度分别进行评分,评分范围为 0~144,护理者苦恼分级评分为 0~60,0 均代表最好[15]。

2.2.6. 统计学方法

使用 SPSS 25.0 软件进行统计分析。符合正态分布的计量资料以均值±标准差表示,组间比较采用两独立样本 t 检验;非正态分布计量资料以中位数(四分位数间距, IQR)表示,组间比较采用 Mann-Whitney U 检验。计数资料以例数(百分比,%)表示,组间比较采用 χ^2 检验或 Fisher 精确概率法。采用单因素 Logistic 回归分析各变量与 VCI 的关联,将具有统计学意义的变量纳入多因素 Logistic 回归模型,以分析 WMH 与 VCI 的独立关联。ROC 曲线分析确定各独立危险因素及联合模型对 WMH 患者 VCI 的识别能力。采用 Spearman 相关和多元线性回归分析 WMH 严重程度对整体及各认知功能领域的独立影响。以双尾 P < 0.05 为差异有统计学意义。

3. 结果

3.1. 两组一般资料比较

共纳入 102 例 WMH 患者,其中 VCI 组 45 例,非 VCI 组 57 例。与非 VCI 组相比,VCI 组患者年龄更高,文盲及脑梗死病史占比更高,抗栓药和他汀类药物使用比例更高,白细胞计数及纤维蛋白原水平更高,差异均有统计学意义(P < 0.05)。影像学上,VCI 组 Fazekas 量表评分更高(P < 0.05)。神经心理学评估显示,VCI 患者 VaDAS-cog 总分及包括记忆、语言、结构性和观念性运用、定向力、执行/注意功能在内的各子项评分明显较高,MMSE 评分较低(P < 0.001)。然而,两组的高血压、糖尿病病史占比,低密度脂蛋白、同型半胱氨酸水平以及 NPI 评分差异均无统计学意义(P > 0.05)。见表 1。

Table 1. Baseline characteristics by vascular cognitive impairment status
表 1. 两组一般资料比较

变量	血管性认知障碍组	非血管性认知障碍组	统计值	P 值
年龄/(岁, IQR)	78.00 (73.00, 81.50)	72.00 (65.50, 75.50)	-4.554	<0.001
文化程度/例(%)			-3.175	0.001
文盲	24 (53.3)	11 (19.3)		
小学	13 (28.9)	28 (49.1)		
初中及以上	8 (17.8)	18 (31.6)		
脑梗死病史/例(%)	32 (71.7)	23 (40.4)	9.576	0.002
使用抗栓药物/例(%)	29 (28.4)	24 (23.5)	5.027	0.025
使用他汀类药物/例(%)	28 (28.5)	24 (23.5)	4.072	0.044
高血压病史/例(%)	36 (35.3)	39 (38.2)	1.732	0.188

续表

糖尿病病史/例(%)	13 (12.7)	16 (15.7)	0.008	0.927
白细胞/(10 ⁹ /L, IQR)	6.00 (4.90, 7.28)	5.52 (4.49, 6.18)	-2.443	0.015
纤维蛋白原/(g/L, IQR)	2.75 (2.39, 3.11)	2.39 (2.17, 2.72)	-2.390	0.017
低密度脂蛋白/(mmol/L, $\bar{x} \pm s$)	1.96 $\pm$ 0.62	2.02 $\pm$ 0.67	-0.451	0.653
高同型半胱氨酸/(μ mol/L, IQR)	13.2 (11.30, 14.6)	12.9 (11.1, 14.7)	-0.758	0.448
Fazekas 评分/(分, IQR)	4.00 (3.00, 5.00)	3.00 (2.00, 3.00)	-4.373	<0.001
NPI 评分/(分, IQR)	6.00 (4.00, 16.00)	5.00 (3.00, 12.00)	-1.393	0.164
MMSE 评分/(分, $\bar{x} \pm s$)	16.29 $\pm$ 4.69	24.23 $\pm$ 2.52	10.240	<0.001
VaDAS-cog 评分/(分, IQR)	49.00 (32.30, 55.70)	23.30 (18.00, 28.70)	-7.290	<0.001
记忆功能/(分, IQR)	32.00 (21.70, 35.70)	13.70 (10.00, 19.00)	-6.815	<0.001
语言功能/(分, IQR)	2.00 (1.00, 3.00)	0.00 (0.00, 3.00)	-5.811	<0.001
结构性运用/(分, IQR)	2.00 (1.00, 2.00)	1.00 (1.00, 1.00)	-4.863	<0.001
观念性运用/(分, IQR)	1.00 (0.00, 2.00)	0.00 (0.00, 0.00)	-5.361	<0.001
定向力/(分, IQR)	3.00 (1.00, 4.00)	0.00 (0.00, 1.00)	-6.452	<0.001
执行/注意功能/(分, IQR)	10.00 (8.00, 10.00)	7.00 (6.00, 8.00)	-5.490	<0.001

3.2. WMH 与 VCI 的二分类 Logistic 回归分析

单因素 Logistic 回归分析显示, WMH Fazekas 评分(OR = 2.244, 95%CI = 1.531~3.290, P < 0.001)是 VCI 的危险因素。为进一步控制混杂因素, 将年龄、文化程度、脑梗死病史、白细胞计数、纤维蛋白原和 Fazekas 评分等单因素分析中具有统计学意义的指标, 纳入多因素 Logistic 回归模型。结果显示, WMH Fazekas 评分每增加 1 分, 患者发生 VCI 的风险增加约 93.6% (OR = 1.936, 95%CI = 1.245~3.012, P = 0.003), 提示 WMH 严重程度是 VCI 的独立危险因素, 见表 2。

Table 2. Logistic regression analysis of WMH Fazekas score and VCI
表 2. WMH Fazekas 评分与 VCI 的二分类 Logistic 回归分析

	回归系数	标准误	Wald 值	OR 值	95%CI	P 值
单因素	0.808	0.195	17.141	2.244	1.531~3.290	<0.001
多因素	0.661	0.225	8.596	1.936	1.245~3.012	0.003

3.3. 各因素及联合模型预测 WMH 患者 VCI 的效能分析

ROC 曲线分析显示, Fazekas 评分、年龄、文化程度、脑梗死病史、白细胞计数、纤维蛋白原以及这六个指标的联合模型均对 WMH 患者 VCI 有预测价值(P < 0.05)。其中联合模型的预测效能最高, 其 AUC 为 0.892, 敏感度为 93.3%, 特异度为 63.2%, 具有临床筛查价值, 见表 3。

3.4. WMH 与认知功能的相关性分析

Spearman 相关分析显示, WMH Fazekas 评分与 MMSE 评分呈显著负相关(r = -0.354, P < 0.001), 与 VaDAS-cog 评分及各子项评分呈显著正相关(r = 0.294~0.441, P < 0.05)。线性回归分析结果表明, 在调整了上述协变量后, WMH Fazekas 评分每增加 1 分, MMSE 评分平均下降 0.826 分, 而 VaDAS-cog 评分平

均上升 2.660 分,在各认知功能子项中,执行/注意功能评分相应上升 0.432 分,语言功能、定向力、观念性运用、结构性运用及记忆功能评分分别上升 0.342 分、0.313 分、0.147 分、0.129 分和 1.297 分($P < 0.05$)。标准化系数(β)进一步表明 WMH 对执行/注意功能的影响最为突出($\beta = 0.254, P = 0.003$)。见表 4。综上所述结果表明,WMH 是认知功能损害的一个显著影响因素,脑白质病变越严重,患者的整体认知功能水平越差,特定的认知功能损害特点表现在执行/注意功能方面。

Table 3. ROC analysis for predicting VCI in WMH patients

表 3. 各因素及联合模型预测 WMH 患者认知障碍的效能分析

项目	AUC	95%CI	P 值	临界点	敏感度/%	特异度/%	约登指数
Fazekas 评分	0.747	0.649~0.845	<0.001	5.5	55.6	80.7	0.363
年龄	0.763	0.669~0.857	<0.001	76.5	57.8	82.5	0.403
文化程度	0.328	0.220~0.435	0.003	-	46.7	19.3	-0.340
脑梗死病史	0.654	0.546~0.761	0.008	0.50	71.1	59.6	0.307
白细胞计数	0.641	0.532~0.751	0.015	6.37	46.7	80.7	0.274
纤维蛋白原	0.638	0.527~0.749	0.017	2.63	64.4	68.4	0.328
联合模型	0.892	0.831~0.952	<0.001	0.252	93.3	63.2	0.565

Table 4. Correlation analysis between WMH Fazekas score and cognitive function assessments

表 4. WMH Fazekas 评分与认知功能评分的相关性分析

认知功能评估	Spearman 相关分析		多元线性回归分析		
	相关系数(r)	P 值	非标准化系数(B)	标准化系数(β)	P 值
MMSE 评分	-0.354	<0.001	-0.826	-0.207	0.005
VaDAS-cog 评分	0.407	<0.001	2.660	0.236	0.001
记忆功能	0.353	<0.001	1.297	0.176	0.026
语言功能	0.330	0.001	0.342	0.232	0.017
结构性运用	0.325	0.001	0.129	0.203	0.041
观念性运用	0.294	0.003	0.147	0.240	0.015
定向力	0.341	<0.001	0.313	0.232	0.012
执行/注意功能	0.441	<0.001	0.432	0.254	0.003

4. 讨论

本研究探讨了 WMH 与 VCI 之间的关联及其特征性的认知损害模式。结果表明,WMH 的严重程度是 VCI 的独立危险因素,且与多个认知领域,尤其是对执行/注意功能损害密切相关。本讨论将根据现有证据,从 WMH 的临床认知表型、其导致认知障碍的影像与网络基础以及病理机制三个层面,系统阐述 WMH 与 VCI 之间的关联。

本研究和大量文献证实,WMH 是整体认知功能下降的强力预测因子。基于社区人群的纵向研究表明,WMH 的进展与整体认知,特别是信息处理速度的下降同步发生[16]。在记忆门诊人群中,WMH 不仅是 SVD 中最活跃的进展性病变,其进展还与临床痴呆评定量表(CDR)评分的加重独立相关[17]。亚洲人群研究同样显示,WMH 负担与认知功能下降存在“剂量-反应”关系[18]。需要警惕的是,WMH 普

遍存在于老年人群中,且其严重程度与认知损害成正比,绝不应被视为良性衰老的标志[19]。而在整体衰退的背景下,WMH也导致了一个相对特征性的认知损害谱,即以执行功能和注意力/处理速度缺陷为核心。本研究显示,WMH对执行/注意功能的负面影响最强。这与既往研究相一致,WMH主要破坏前额叶-皮质下环路,导致认知处理速度减慢、定时转换能力下降和抑制控制功能减弱[20][21]。一项纵向研究进一步细化,发现重度WMH与注意力、执行功能的加速衰退尤为相关[22]。系统综述也指出,注意力和执行功能是受WMH影响最大的认知领域[23]。WMH的认知影响在不同疾病中可能存在共性,例如在帕金森病和额颞叶痴呆中,伴随的WMH也会加剧整体的认知损害[24][25]。

值得注意的是,WMH对认知功能的影响与病变的解剖分布和微观结构密切相关。神经病理学指出,常规MRI可见的WMH仅是广泛性脑损伤的“冰山一角”,其周围体积巨大、微观结构已受损的“表观正常白质”才是导致网络连接中断的主因[26]。多模态MRI研究证实,WMH区域及其周围白质的平均扩散率(MD)升高,提示早期水肿和微观结构破坏[27][28]。此外,空间分布具有决定性意义。脑室周围白质是长联络纤维、胼胝体纤维和长投射纤维的“交通要道”,此区域的病变比深部白质病变更易导致大规模的皮层-皮层下网络断开[29]。一项针对遗忘型轻度认知障碍患者的研究发现,脑室周围区域(尤其是双侧额角、顶叶部和枕角)的白质高信号体积,与注意力和执行功能损害显著相关,而深部白质区域的病变则未显示出这种关联[30]。另一项采用创新性“病变网络映射”的研究从机制上阐明,WMH会选择性且强效地破坏与注意力控制相关的背侧和腹侧注意网络,从而直接导致注意涣散、任务切换困难等VCI核心症状[31]。这种结构损伤会触发大脑网络的复杂重组与代偿。多模态影像证据表明,VCI患者在白质结构连接性下降的同时,静息态功能网络的整体拓扑结构可能保持稳定,但在默认模式网络等相关脑区会出现异常增强的结构-功能耦合。值得注意的是,这种增强的耦合与更差的记忆和更慢的信息处理速度相关,可能代表了一种低效的、最终与不良认知表现相关的代偿努力[32]。此外,较高的身体和认知储备可能通过增强前额顶叶网络的整合与灵活性,帮助个体抵抗WMH带来的功能损害[33]。

上述网络连接的中断,根源在于WMH所代表的白质微观结构破坏。而这一破坏本身,则是一个涉及多重血管病理机制的动态过程。慢性脑低灌注被认为是这一过程的始动环节和核心驱动因素,它连接了上游的血管危险因素与下游的神经炎症、氧化应激等一系列病理改变,最终导致白质损伤[34]。动物模型直接证实,慢性低灌注可激活小胶质细胞,引发神经炎症和白质微观结构破坏,从而造成空间记忆与执行功能缺陷[35]。而清除小胶质细胞或使用秋水仙碱抑制神经炎症,则可有效缓解这些病理改变与认知障碍[36][37],明确了炎症在此通路中的关键作用。

此外,低灌注及其引发的炎症直接损害血脑屏障(BBB)的完整性。BBB破坏不仅是WMH形成与发展的重要机制[38],其本身也可能是认知下降的直接诱因。研究表明,BBB渗漏,尤其是在外观正常的白质中,可能与早期、细微的执行和处理速度下降直接相关[39]。渗漏的纤维蛋白原等大分子会驱动血管周围炎症,进一步加剧小胶质细胞损伤和脱髓鞘[40][41]。这种血管源性损伤在细胞层面表现为星形胶质细胞的“碎裂样病变”,该病变与BBB破坏密切相关,是连接血管病理与认知障碍的关键细胞事件[42]。

近期的研究揭示,类淋巴系统功能障碍是另一个重要机制。WMH相关的认知损害与类淋巴清除效率降低及区域性脑血管反应性下降显著相关[43]。一项神经影像学研究表明,较差的类淋巴功能差与较低的皮层厚度显著相关,提示类淋巴清除障碍可能导致毒性蛋白堆积,加速神经元丢失和皮层变薄[25]。此外,外周免疫系统也参与其中,白细胞中涉及内皮功能障碍、脱髓鞘及炎症反应的基因表达与WMH的进展相关[44],而血清中特定的炎症相关脂质代谢物(如sEH活性标志物)也与WMH的严重程度及执行功能损害关联[45],为寻找外周血生物标志物提供了线索。

本研究存在一定的局限性。首先,本研究为横断面研究,仅能反映WMH与VCI在同一时间点的关联性,无法确定因果关系。其次,采用改良Fazekas量表进行视觉分级,虽临床常用,但属于半定量方法,

无法精确量化 WMH 的体积、分布及微观结构变化,可能影响对 WMH 严重程度的准确评估。最后,研究未对患者进行纵向追踪,无法评估 WMH 的进展与认知功能变化的动态关系,也无法预测 WMH 对 VCI 发展的长期影响。未来研究需通过纵向设计,结合多模态神经影像和外周生物标志物,动态观察 WMH 进展与认知衰退的轨迹,从而更早识别高危个体,并探索针对血管保护、炎症调控或类淋巴功能改善的精准干预策略,以延缓或预防血管性认知障碍的发生与发展。

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