·专题综述·

脑小血管病早期诊断及预后评估生物学标志物研究进展

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【摘要】 脑小血管病是脑卒中、痴呆和死亡的重要危险因素，严重危害老年人生命健康和生活质量。脑小血管病起病隐匿，缺乏早期诊断方法及干预措施，探究脑小血管病早期诊断及预后评估标志物对疾病的预防与治疗至关重要。本文综述脑小血管病早期诊断及预后评估的影像学和实验室标志物，以为脑小血管病预防、诊断及治疗策略的制定提供新的思路。

【关键词】 大脑小血管疾病； 磁共振成像； 生物标记； 综述

Research progress on biomarkers of early diagnosis and prognosis of cerebral small vessel disease

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【Abstract】 Cerebral small vessel disease (CSVD) is an important risk factor for stroke, dementia and death, which seriously endangers the health and quality of life of the elderly. The onset of CSVD is insidious and there is a lack of early diagnosis methods and interventions, so the search for markers that can provide early warning of CSVD and prognosis assessment is very important for the prevention and treatment of the disease. This article reviews imaging and laboratory biomarkers for early diagnosis and prognosis of CSVD, in order to provide new ideas for the formulation of prevention, diagnosis and treatment strategies related to the disease.

【Key words】 Cerebral small vessel diseases; Magnetic resonance imaging; Biomarkers; Review

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脑小血管病(CSVD)是脑部小血管病变引起的多种临床表现和影像学改变的临床综合征[1]，MRI典型表现包括近期皮质下小梗死(RRSI)、腔隙(lacunes)、脑白质高信号(WMH)、扩大的血管周围间隙(EPVS)和脑微出血(CMBs)[2]。脑小血管病发病隐匿且逐渐进展，影像学异常和临床症状存在较大异质性和滞后性。随着人口老龄化加剧，脑小血管病患病数迅速增多，成为亟待解决的临床和公众健康问题。因此，寻找新的、有意义的脑小血管病生物学标志物，有助于疾病早期精准诊断、病情进展预测和评估，进而改善患者预后。基于此，本文拟就脑小血管病早期诊断及预后评估的影像学和实验室标志物进行综述，以推进脑小血管病相关预

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防、诊断及治疗策略制定的发展。

一、脑小血管病影像学标志物

目前，脑小血管病的诊断主要结合临床特征和MRI表现，但常规MRI如T_1WI、T_2WI、FLAIR成像等尚无法早期预警脑小血管病[3]，扩散张量成像（DTI）、动态对比增强MRI（DCE-MRI）、静息态fMRI（rs-fMRI）、动脉自旋标记（ASL）、体素内不相干运动成像（IVIM）等结构和功能影像学技术的不断发展，对探究脑小血管病早期诊断及预后评估的影像学标志物发挥巨大作用。

1.脑小血管病脑损伤的结构性影像学标志物

（1）DTI相关影像学标志物：DTI是一种通过水分子扩散运动反映脑白质微结构的MRI技术，可以无创追踪白质纤维束走行并评估其完整性[4]。脑小血管病是老年人脑白质损伤的主要原因[5]，DTI对常规MRI未检测到的早期广泛脑白质病变十分敏感，对脑小血管病相关脑白质损伤的早期诊断至关重要[6-8]。评价个体病变的最佳DTI标志物仍未确定，目前较常用的是平均扩散率峰宽（PSMD），该参数是基于DTI及DTI直方图分析白质纤维束骨架的影像学标志物，对检测脑小血管病核心病变（脑白质高信号）十分敏感，可以有效预测脑小血管病的发生[9-11]。研究显示，脑小血管病患者PSMD值显著高于健康对照者（$P<0.001$）；年龄调整的线性回归分析显示，脑小血管病患者和健康对照者PSMD值均与脑白质高信号体积呈正相关（$\beta=0.750$，$P<0.001$；$\beta=0.690$，$P<0.001$）；包含脑小血管病所有MRI定量标志物的多重线性回归分析亦显示，脑小血管病患者PSMD值与脑白质高信号体积呈正相关（$\beta=0.660$，$P<0.001$）[12]，提示PSMD可以反映脑白质损害程度，进而作为脑小血管病早期诊断的影像学标志物。此外，PSMD还可用于评估脑小血管病进展及预后。该项研究进一步以认知功能为因变量行多重线性回归分析，发现PSMD值与脑小血管病患者信息处理速度呈负相关（$\beta=-1.080$，$P=0.004$），提示PSMD可预测脑小血管病认知功能减退[12]。亦有研究显示，脑小血管病患者PSMD值高于阿尔茨海默病患者、轻度认知损害患者和正常老年人；且PSMD值较高的脑小血管病患者信息处理速度减慢（95%CI：-0.420～-0.030，$P=0.030$），脑白质高信号体积增大（95%CI：0.480～1.000，$P<0.001$），提示PSMD可有效预测脑小血管病相关认知功能障碍，表明脑白质损害在脑小血管病相关认知功能障碍中发挥重要作用[13]。其他DTI参数亦可作为脑小血管病患者痴呆转化标志物。最近一项前瞻性队列研究同时对PSMD、常规脑白质直方图平均扩散率（中位数）、基于常规脑白质直方图测量的主成分派生测量、DTI分割θ和全球结构网络效率度量与痴呆的关系进行评估，结果显示，转化为血管性痴呆和阿尔茨海默病的重度脑小血管病患者上述基线DTI参数存在差异（均$P<0.05$），提示上述DTI参数可以作为预测脑小血管病患者痴呆转化率的标志物[14]；部分各向异性（FA）、定量磁化率等DTI参数均可作为脑小血管病相关认知功能障碍预后评估的标志物[15-17]；将DTI参数与图论分析相结合，从DTI图像中获得有价值的结构连通性指标，可预测脑小血管病患者认知功能减退、痴呆转化率，甚至全因死亡率，具有极大应用前景[5,18]。（2）DCE-MRI相关影像学标志物：DCE-MRI是一种通过测量钆对比剂在血浆和脑组织中随时间的变化而评估血脑屏障完整性的MRI标志物，业已广泛应用于血脑屏障完整性破坏相关中枢神经系统疾病的研究[19]。脑小血管病患者血脑屏障通透性增加的数量级较小，MRI增强扫描难以检测到液体和对比剂外渗，而DCE-MRI可检测到血脑屏障通透性的细微变化，用于脑小血管病的早期诊断[19]。一项研究采用示踪剂动力学分析量化DCE-MRI测量的渗漏率-表面积（PS）、血脑屏障渗漏估计值和血浆体积，结果显示，脑白质信号正常而血脑屏障损伤时PS值升高，脑白质高信号患者PS值更高，提示PS可以作为脑小血管病早期诊断的影像学标志物[20]。DCE-MRI还可用于评估脑小血管病进展。对脑小血管病患者行基线DCE-MRI检查，采用血脑屏障渗漏量量化正常脑白质、脑白质高信号、皮质灰质和脑深部灰质血脑屏障通透性，并探究其与认知功能减退之间的关系，经过2年随访发现，基线时较高的血脑屏障渗漏量与2年内整体认知功能（$\beta=1.340$，$P<0.001$）、执行功能（$\beta=1.900$，$P=0.003$）和记忆力（$\beta=1.860$，$P=0.018$）减退严重程度呈正相关，尤其与执行功能的关联性最高，提示DCE-MRI测量的血脑屏障渗漏量可以作为脑小血管病预后评估标志物[21]。

2.脑小血管病血管损伤的功能性影像学标志物

（1）rs-fMRI相关影像学标志物：rs-fMRI是基于血氧水平依赖（BOLD）信号的MRI技术，通过间接测量神经元活动并根据脑区之间自发低频波动的强度和同步性以反映各脑区之间的功能连接（FC），

可用于构建神经功能网络，进而探究脑小血管病患者神经功能变化[22]。rs-fMRI构建的神经功能网络改变可早期诊断脑小血管病[16]。一项单中心研究表明，脑默认网络（DMN）、感觉运动网络和额顶控制网络中自发神经元活动改变与脑微出血灶数目相关，提示其可作为脑小血管病的诊断标志物[23]。Blair等[24]采用rs-fMRI评估脑小血管病患者脑血管反应性（CVR），发现脑血管反应性较低与脑白质高信号体积较大呈正相关（$P=0.020$），静脉搏动性较大与基底节区血管周围间隙扩大呈正相关（$P=0.020$）。Clancy等[25]的前瞻性纵向研究进一步证实，rs-fMRI测量的脑血管反应性降低是脑小血管病的危险因素，提示其可作为脑小血管病的早期诊断标志物。rs-fMRI亦可用于评估脑小血管病进展。有研究采用rs-fMRI对比分析经单硝酸异山梨酯和西洛他唑治疗前后脑小血管病患者脑血管反应性，发现单硝酸异山梨酯（$\beta=0.021$，95%CI：0.003～0.040；$P=0.027$）和西洛他唑（$\beta=0.035$，95%CI：0.014～0.056；$P=0.003$）单药治疗组及联合治疗组（$\beta=0.021$，95%CI：0.005～0.037；$P=0.014$）脑血管反应性均增加，证实rs-fMRI测量脑血管反应性以评估脑血管功能在临床试验中具有可行性，提示其可作为脑小血管病的预后评估标志物[26]。最近一项单中心随机对照试验表明，与不伴步态障碍患者相比，伴步态障碍的脑小血管病患者感觉运动网络和额顶控制网络低频振幅（ALFF）值降低，脑默认网络ALFF值升高，辅助运动区之间FC值降低[27]，提示上述rs-fMRI参数可预测脑小血管病患者步态改变。另一项研究采用rs-fMRI探究小脑在脑小血管病发病中的作用，发现伴认知功能减退的脑小血管病患者小脑灰质体积减少，双侧小脑小叶Ⅳ区与左侧前扣带回之间FC值降低，证实神经功能网络改变与脑小血管病相关认知功能障碍相关，可以作为脑小血管病相关认知功能障碍的新的影像学标志物[28]。（2）ASL相关影像学标志物：ASL是一种灌注加权的MRI技术，以动脉血中水分子作为内源性示踪剂，结合动力学模型获得脑血流量。脑灌注异常是脑小血管病的常见表现，脑小血管病的发生发展伴随脑血流量变化[29]。一项回顾性研究显示，脑小血管病患者脑深部血流量减少与脑小血管病影像学负荷增加呈正相关（$OR=0.894$，95%CI：0.811～0.985；$P=0.024$），提示脑血流量减少可以作为脑小血管病的诊断标志物[30]。随后研究显示，健康老年人和存在脑小血管病风险的老年人脑血流量与脑白质高信号总体积呈负相关，提示脑血流量减少可有效预警脑小血管病[31-32]。ASL也可用于脑小血管病预后评估。一项研究对基因诊断为伴有皮质下梗死和白质脑病的常染色体显性遗传性脑动脉病（CADASIL）的22例患者进行为期2年的随访，结果显示，基线脑血流量较低的CADASIL患者2年内脑白质高信号体积（$P<0.001$）和脑微出血灶数目（$P<0.001$）显著增加，提示脑血流量可预测CADASIL进展[33]。上述影像学参数与ASL测量的血脑屏障渗漏率和脑血管反应性互补，可以作为脑小血管病预后评估标志物[34-35]。此外，通过与深度学习相结合，ASL测量的血流动力学标志物对脑小血管病的评估准确性进一步提高[36-38]，加速其临床转化。（3）IVIM相关影像学标志物：IVIM是一种磁敏感加权成像（SWI）技术，其在不同扩散权重下采集多个图像，可以定量描述脑微观结构的灌注和扩散，旨在区分脑实质中水分子扩散及其与脑灌注相关的伪扩散运动[39]。脑小血管病宏观影像学标志物变化缓慢，短期进展难以监测，IVIM对微观结构的独特易感性可用于脑小血管病的预后评估[40]。IVIM结合光谱扩散模型在脑小血管病患者的病变易发区域可识别出位于传统扩散与伪扩散之间的中间扩散成分，中间扩散体积分数增加与脑白质高信号和扩大的血管周围间隙呈正相关，可作为脑小血管病进展评估标志物[41]。最近一项纵向研究采用IVIM成像监测脑小血管病患者2年内脑白质高信号周围区域的实质扩散率，可见脑白质高信号周围区域实质扩散率显著增加，且该变化早于脑白质高信号体积扩大，提示脑白质高信号周围区域实质扩散率可以作为脑小血管病的预后评估标志物[42]。

3. 其他影像学标志物　7T MRI是超高场强MRI技术，通过提高信噪比实现更高的时间分辨率和组织对比度，可以更早发现脑小血管病相关血管和脑实质损伤[43]，具有一定的早期诊断价值。继2010年首次通过7T MRI行豆纹动脉成像以来[44]，研究者发现脑小血管病患者豆纹动脉分支减少（$P=0.003$）[3]。亦有研究利用7T相位对比MRI直接测量脑内穿支动脉流速，发现遗传性脑小血管病患者豆纹动脉流速减慢（$P<0.001$），提示其可作为脑小血管病的诊断标志物[45]；脑小血管病患者基底节区和半卵圆中心小穿支动脉流速显著增快，表明脉动流速可预警脑小血管病[46]。此外，7T MRI可

以使位于血管壁的病理改变可视化，在发生永久性脑实质损伤前即可捕捉到动脉粥样硬化，而后者与脑白质高信号和皮质下微梗死等均具有相关性，可作为脑小血管病的早期诊断标志物[47]。

二、脑小血管病实验室标志物

鉴于脑小血管病发病的多因性和临床表现的复杂性，深入了解其发病机制有助于进一步明确病程中生化改变，因此，从发病机制出发探寻脑小血管病潜在实验室标志物以实现疾病的早期高效识别和干预成为新的热点。

1.血液标志物　血液标志物是目前脑小血管病研究最广泛的外周生物学标志物。现有证据支持血管内皮功能障碍、血脑屏障损伤和炎症反应是脑小血管病的主要病理生理学机制[48-49]，探究脑小血管病发病前后血液内相关通路分子变化，有助于发现脑小血管病新的诊断标志物。(1)血管内皮功能障碍和血脑屏障损伤标志物：血管内皮功能障碍是脑小血管病的首要病理生理学机制，可造成脑血流量减少、血管损伤和脑血流自动调节能力丧失[50]。血脑屏障通透性增加可导致免疫细胞和有害毒素进入脑实质，进一步损害血管内皮细胞，促进脑小血管病进展[51]。早期功能失调的血管内皮细胞分泌各种分子，如血管性血友病因子(vWF)、热休克蛋白90α(HSP90α)、细胞间黏附分子-1(ICAM-1)、血管细胞黏附分子-1(VCAM-1)、不对称二甲基精氨酸、酸性鞘磷脂酶、选择素和基质金属蛋白酶(MMPs)等，可直接诱发血管损伤，损伤血脑屏障和脑白质，提示上述血管内皮损伤标志物可早期诊断脑小血管病[52-55]。高同型半胱氨酸血症亦与血管内皮细胞损伤有关，是动脉粥样硬化和心脑血管疾病的危险因素[56]。研究发现，血清同型半胱氨酸水平与脑小血管病的发生呈剂量依赖关系，可用于预警脑小血管病[57]。随后的一项前瞻性研究显示，高同型半胱氨酸水平是腔隙形成的危险因素(OR = 2.140，P < 0.0001)、与脑萎缩呈负相关(β = - 0.550，P = 0.004)，且具有一定的遗传易感性[58]。因此，加强对存在脑小血管病高遗传风险人群的同型半胱氨酸监测有助于其早期诊断。内皮衍生外泌体(EDE)在维持血管内皮细胞功能和炎症调节方面发挥重要作用[59]。研究发现，脑白质高信号患者血浆包括葡萄糖转运蛋白-1、大中性氨基酸转运蛋白-1、通透性糖蛋白和NOSTRIN蛋白在内的内皮衍生外泌体水平显著升高[60]，提示内皮衍生外泌体与脑小血管病具有一定相关性，尚待进一步研究以期用于脑小血管病的早期诊断。(2)炎症标志物：炎症是脑小血管病发病机制的关键组成部分，有关炎症可促使脑小血管病进展并导致严重后果的证据日益增多。炎症标志物可分为系统炎性因子和血管炎性因子，前者包括C-反应蛋白(CRP)、白细胞介素-6(IL-6)、肿瘤坏死因子-α(TNF-α)和降钙素原(PCT)等，后者即为传统意义的血管内皮损伤标志物。既往研究大多致力于探究单一炎症标志物与脑小血管病影像学表现之间的相关性[61]，但实际上炎症标志物并非单独作用，同时测定不同炎症反应途径的多种成分可进一步完善脑小血管病标志物诊断谱。最近的一项横断面研究同时测定包括超敏C-反应蛋白(hs-CRP)、IL-6、VCAM-1等在内的15种参与炎症级联反应的血液标志物，结果显示，血管炎性因子水平升高与脑白质高信号体积增大和腔隙形成呈正相关，分别为VCAM-1与脑白质高信号体积(P = 0.005)、总同型半胱氨酸与腔隙形成(P < 0.001)、系统炎性因子与髓质深静脉(P = 0.006)，尤以hs-CRP与脑白质高信号体积和腔隙形成的相关性最强[62]，提示上述炎症标志物可作为脑小血管病的早期诊断标志物。炎症标志物亦可用于脑小血管病的病情评估。超氧化物歧化酶(SOD)和脂蛋白相关磷脂酶A2(Lp-PLA2)是具有强抗炎活性的炎性因子。新近研究发现，血浆Lp-PLA2(OR = 1.014，P = 0.025)和SOD(OR = 0.933，P = 0.001)水平降低是脑小血管病相关认知功能障碍的危险因素[63-64]，提示其可作为脑小血管病预后评估的新的炎症标志物。(3)神经损伤标志物：代表神经变性的外周血神经丝轻链(NfL)可作为脑小血管病的预后评估标志物[65]。研究显示，血清NfL与脑白质高信号体积、腔隙和脑微出血灶数目相关，且血清NfL水平升高的脑小血管病患者痴呆风险更高[66]，动态增加的血清NfL水平预示脑小血管病快速进展[67]，但因其在阿尔茨海默病、肌萎缩侧索硬化、帕金森病等多种神经系统变性疾病中均表达上调，暂不具有鉴别诊断价值。(4)代谢相关标志物：特定氨基酸和脂肪酸水平可用于脑小血管病早期诊断。业已证实，高密度脂蛋白胆固醇、低密度脂蛋白胆固醇和甘油三酯水平与新发腔隙、脑白质高信号体积具有相关性[68]。一项横断面研究对比脑小血管病患者与健康对照者的血清氨基酸谱和脂肪谱差异，经多因素Logistic回归分析显示，血清丙氨酸(P = 0.044)和甘氨酸/丙

氨酸比值(P = 0.002)增加、甘氨酸降低(P = 0.031)是脑小血管病的危险因素[69],说明上述指标可作为脑小血管病的预警标志物。鉴于该项单中心研究的样本量较小,且横断面研究无法得出相关标志物与脑小血管病的因果关系,未来尚待多中心大样本队列研究进一步探究二者关系。(5)凝血标志物:凝血标志物在脑小血管病诊断中的作用已得到越来越多的关注。除vWF外,较高水平的血栓调节素、凝血酶-抗凝血酶和D-二聚体与脑白质高信号呈正相关,未来有望成为早期诊断脑小血管病的新的标志物[68,70]。

2.尿液标志物 脑小血管病的发生可伴发肾功能障碍。Meta分析显示,肾功能障碍与脑小血管病的发生呈正相关(RR = 1.770,95%CI:1.400~2.240;I^2 = 0.000%)[71]。白蛋白尿提示肾脏和大脑共存微血管病变,且白蛋白尿与脑小血管病的发生具有相关性[72],表明全身性微血管病变标志物可用于评估脑小血管病血管损伤。一项前瞻性队列研究显示,微量白蛋白尿是腔隙性梗死的危险因素(HR = 1.750,95%CI:1.120~2.720;P = 0.019)[73],进一步证实白蛋白尿对脑小血管病的预警作用。

3.粪便标志物 脑-肠轴是胃肠道微生物群与大脑之间的双向信号转导通路,具有维持人体与微生物群平衡的作用[74]。越来越多的证据表明,肠道微生物群与心血管病和神经系统变性疾病之间存在相关性[75-76],可用于脑小血管病的诊断。基于自发性高血压大鼠模型的研究显示,肠道微生物群通过破坏血脑屏障完整性参与脑小血管病的发生,其机制可能包括菌群紊乱促进肠道炎症、肠道炎症进展为全身炎症进而通过脑-肠轴诱发神经炎症[77]。一项日本横断面研究发现,肠道微生物群紊乱与脑白质高信号相关[78];Cai等[79]发现,动脉粥样硬化性脑小血管病患者影像学总负荷和蒙特利尔认知评价量表(MoCA)评分与肠道微生物群紊乱相关,在其团队构建的脑小血管病预测模型中增加肠道微生物群相对丰度这一指标,可显著提高其预测效能。故改变生活方式以重塑肠道微生物群进而缓解炎症反应,有利于脑小血管病的预防与治疗[80]。

脑小血管病患病率逐年增加,但仍缺乏准确的早期诊断策略和预后评估方案。脑小血管病的病理生理学机制较为复杂,相关生物学标志物大多缺乏特异性,因此,新的特异性生物学标志物对脑小血管病的早期诊断及预后评估显得极为重要。未来尚待进一步探究各种生物学标志物在不同脑小血管病亚型和适用病程阶段的表达变化;此外,探究基因、环境和个体差异等因素影响下的脑小血管病早起诊断及预后评估标志物亦颇具研究前景。总之,提高脑小血管病生物学标志物的特异性及其在诊断、治疗及预后评估中的应用价值是今后重点研究方向。

利益冲突 无

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（本文编辑：袁云）

《中国现代神经疾病杂志》关于谨防伪造微信采编中心的声明

《中国现代神经疾病杂志》编辑部近期发现伪造本刊微信采编中心的非法行为，微信号码jiayou1583，昵称知了，伪造《中国现代神经疾病杂志》采编中心。该微信号以核对作者信息为由，请我刊作者添加其为微信好友，借以窃取相关信息甚至索取审稿费和版面费等，此举对我刊及广大作者、读者造成严重不良影响。

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