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·综述·

血清学标志物预测青年缺血性卒中复发的研究进展

张曼[1]，周艳容[2]，张小波[3]，童雪晴[3]
1. 青海大学研究生院，青海 西宁 810016
2. 广州国际旅行卫生保健中心，广东 广州 510000
3. 中南大学湘雅医学院附属常德医院（常德市第一人民医院），湖南 常德 415000

摘　要：近年来，青年缺血性卒中发病率显著上升，其长期复发风险备受关注。现有研究表明，神经丝轻链（NfL）、胶质纤维酸性蛋白（GFAP）、白细胞介素-6（IL-6）、可溶性CD40配体（sCD40L）、D-二聚体/纤维蛋白原比值（DFR）等血清学标志物可反映神经损伤、胶质细胞活化、炎症反应、血小板激活及凝血－纤溶系统失衡等关键病理过程，也为复发风险预测提供了潜在生物学基础。此外，新兴的外泌体microRNA谱和蛋白质组学指标（如钙结合蛋白／载脂蛋白C3）等的发现，进一步深化了对卒中复发分子机制的认知。该文基于最新国内外研究进展，聚焦上述血清学标志物（涵盖传统与新型标志物）与青年缺血性卒中复发的关联，深入剖析其内在作用机制，旨在为临床精准评估青年缺血性卒中患者的复发风险，制定个体化二级预防策略提供科学依据。

关键词：缺血性卒中；复发；风险评估；血清学标志物；青年

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Research advances in serological markers for predicting the recurrence of ischemic stroke in young adults

ZHANG Man[1], ZHOU Yanrong[2], ZHANG Xiaobo[3], TONG Xueqing[3]
1. Graduate School of Qinghai University, Xining, Qinghai 810016, China
2. Guangzhou International Travel Health Care Center, Guangzhou, Guangdong 510000, China
3. Changde Hospital, Xiangya School of Medicine, Central South University (Changde First People's Hospital), Changde, Hunan 415000, China
Corresponding author: TONG Xueqing, Email: 1010346339@qq.com

Abstract: In recent years, there has been a significant increase in the incidence rate of ischemic stroke among young adults, and the risk of long-term recurrence has attracted much attention. Current studies have shown that serological markers, such as neurofilament light chain, glial fibrillary acidic protein, interleukin-6, soluble CD40 ligand, and D-dimer/fibrinogen ratio, can reflect the key pathological processes of nerve injury, glial cell activation, inflammatory response, platelet activation, and coagulation-fibrinolytic system imbalance, and these markers also provide a potential biological basis for predicting the risk of recurrence. Furthermore, the identification of emerging exosomal miRNA profiles and proteomic indicators (such as S100A12 and ApoC3) has further deepened the understanding of the molecular mechanisms for the recurrence of stroke. Based on the latest research advances in China and globally, this article focuses on the association between the above serological markers (covering both traditional and novel markers) and the recurrence of ischemic stroke in young adults and analyzes their underlying mechanisms of action, in order to provide a scientific basis for accurately assessing the risk of recurrence in young patients with ischemic stroke and developing individualized secondary

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作者简介：张曼（1998—），女，在读硕士研究生，主要从事脑血管病基础和临床研究。Email：1960582236@qq.com。
通信作者：童雪晴（1991—），女，主治医师，医学硕士，主要从事神经电生理基础和临床研究。Email：1010346339@qq.com。

prevention strategies.

Keywords: ischemic stroke; recurrence; risk assessment; serological markers; young adults

青年缺血性卒中特指在18～50岁发生的缺血性脑血管事件,其发病率近年来呈显著上升趋势[1]。1990年至2019年青年缺血性卒中的年龄标化发病率总体呈下降趋势(降幅0.5%),但中国同期发病率却上升了15.5%[2]。尽管该群体急性期病死率低于老年卒中患者,但15年累积病死率高达16.4%,提示初始致病因素可能具有持续性生物学效应[3-4]。青年患者缺乏典型血管危险因素,可能存在特异性代谢调控异常,为发病机制研究提供新方向[5]。

血清学标志物凭借其无创、可重复检测及良好的成本效益比,在青年缺血性卒中复发预测研究中展现出显著优势。相较于影像学或电生理检测技术,血清标志物不仅可反映局部神经损伤,更能系统性评估全身性病理生理过程,如炎症级联反应[6]、氧化应激[7]、血脑屏障损伤[8],为复发风险分层提供多维生物学信息。

本文聚焦青年缺血性卒中复发的血清学标志物,系统梳理神经损伤、炎症、凝血-纤溶、代谢相关标志物以及新型生物分子学标志物的研究进展,深入剖析这些标志物与青年缺血性卒中复发的关系。本文旨在为临床医生提供复发监测策略,推动多模态生物标志物预测模型的构建,为最终实现青年缺血性卒中患者的精准二级预防,以期为降低复发致残率并改善长期预后提供帮助。

1　神经损伤标志物

1.1　神经丝轻链与神经损伤和复发风险的关系

神经丝轻链(neurofilament light chain, NfL)作为神经元轴突损伤的特异性生物标志物,其血清水平升高直接反映神经轴突完整性破坏。青年缺血性卒中患者血清NfL持续升高,不仅提示急性期神经损伤,更与长期神经退行性病变密切相关,可表现为白质纤维素萎缩速率加快和全脑容量减少。值得注意的是,创伤性脑损伤队列研究显示,损伤后8个月血清NfL水平对5年后的脑白质体积减小及脑容量年化损失具有显著预测价值[9]。这一发现为NfL在卒中复发风险评估中的跨疾病适用性提供了重要依据[10]。研究显示,部分青年缺血性卒中患者合并遗传性或早发性脑小血管病(如脑淀粉样血管病),其持续升高的NfL水平可反映慢性神经轴突损伤程度,间接提示脑淀粉样血管病变等血管内皮功能障碍的进展,进而形成缺血性卒中复发的恶性循环[11-12]。

1.2　胶质纤维酸性蛋白与缺血性卒中的关联

胶质纤维酸性蛋白(glial fibrillary acidic protein, GFAP)是星形胶质细胞活化的标志物,其升高提示血脑屏障破坏、炎症反应及胶质瘢痕形成。慢性期GFAP波动可能与继发性神经炎症相关,炎症微环境可能促进血管内皮损伤,增加血栓形成风险[9]。在青年缺血性卒中患者中,血清GFAP持续升高可能提示慢性脑损伤或未控制的血管危险因素(如高血压、动脉炎),这些均是缺血性卒中复发的潜在危险因素。研究显示,GFAP与NfL联合可提高对中重度缺血性卒中患者功能预后的预测准确性[13]。

1.3　NfL与GFAP的协同预警价值

NfL和GFAP通过差异化的病理机制参与青年缺血性卒中复发进程。当二者血清水平同步升高时,提示神经炎症持续活跃,与血管再发事件相关[13-14]。青年缺血性卒中患者复发可能与隐匿性血管病变(如未诊断的脑小血管病或炎症性血管病)有关。定期检测NfL和GFAP水平有助于识别亚临床脑损伤,指导青年缺血性卒中的二级预防[15]。

2　炎症标志物

2.1　白细胞介素-6在缺血性卒中复发中的关键作用

白细胞介素-6(interleukin-6, IL-6)水平升高与缺血性卒中不良功能结局和死亡风险显著相关,调整后的风险比可达3.1[16]。另外,随着IL-6水平增加,缺血性卒中复发风险及主要血管事件风险会显著上升,这种现象在动脉粥样硬化或小血管病变患者中更为明显[17]。IL-6还被证实可独立预测缺血性卒中复发风险,并可能通过介导缺血性卒中复发,间接影响神经功能的恢复,提示其可作为炎症负荷的直接生物学标志物[18]。

2.2　可溶性CD40配体与动脉炎性病因的关联

血小板表面可溶性CD40配体(soluble CD40 ligands, sCD40L)的高表达与缺血性卒中后神经功能恢复不良密切相关,其水平升高可能反映了血管内皮炎症或动脉粥样硬化斑块的不稳定性[19]。在颈动脉狭窄或动脉粥样硬化患者中,sCD40L的表达增加与斑块炎症活动相关,这可能提示动脉炎性病因的存在[20]。

2.3　IL-6和sCD40L联合检测的临床意义

IL-6和sCD40L分别代表不同炎症通路,即全身性炎症反应与血管内皮/血小板活化,二者联合检测可提高对青年缺血性卒中动脉炎性病因亚型的识别能力。在治疗指导方面,IL-6和sCD40L水平持续升高的患者可能存在残留炎症风险,适合早期接受免疫调节治疗[21]。

3　凝血-纤溶指标

3.1　青年缺血性卒中复发的特异性

青年缺血性卒中患者的长期复发风险显著高于老年患者,部分归因于未被识别的高凝状态,如遗传性或获得性血栓形成倾向[22]。在这类患者中,D-二聚体/纤维蛋白原比值(D-dimer to fibrinogen ratio, DFR)可能通过反映潜在的高凝机制,间接提示复发风险。此外,颅内动脉低密

度钙化、点状钙化和颈动脉斑块内新生血管在青年缺血性卒中复发患者中更为常见[23]。这些结构性病变可能通过促进局部血栓形成,与DFR反映的高凝状态协同作用,增加缺血性卒中复发风险。

3.2　病理生理的机制支持

D-二聚体反映纤溶活性,而纤维蛋白原反映凝血活性。因此,DFR可用于动态评估血液凝血与纤溶系统的平衡状态。通常情况下,前者升高常伴随后者消耗或代偿性增加,提示凝血系统激活和纤溶系统代偿不足的失衡状态。这种失衡状态易导致血栓形成或再梗死,而DFR可量化这一失衡程度[24-26]。例如,在脑静脉血栓中,高DFR与疾病严重程度和不良预后直接相关[24]。所以,相较于D-二聚体或纤维蛋白原,DFR能更准确地反映血栓形成风险[27-28]。

3.3　DFR可能预测缺血性卒中复发

一项荟萃分析证实,高D-二聚体水平与缺血性卒中复发风险独立相关,且该关联可能比纤维蛋白原更显著[29]。结合另一项研究的结果,提示DFR可能通过反映D-二聚体动态变化增强预测价值[30]。

4　代谢标志物

4.1　同型半胱氨酸的神经毒性作用

同型半胱氨酸(homocysteine, Hcy)是甲硫氨酸代谢中间产物。Hcy水平升高会促进自由基生成,从而损伤血管内皮细胞,加剧缺血性卒中后再灌注损伤[31]。核因子κB通路触发神经炎症,导致海马区神经元凋亡[32]等,促进动脉粥样硬化及血栓形成,进而增加缺血性卒中复发风险[33]。

4.2　叶酸的神经保护作用

叶酸是一碳代谢的关键辅因子,参与核苷酸合成、甲基化反应和氨基酸稳态[34]。通过调节N-甲基-d-天门冬氨酸受体活性和表达,抑制脑缺血后突触功能障碍及兴奋性神经元死亡,减轻认知损伤。动物实验表明,叶酸预处理可改善脑缺血再灌注损伤后的神经元功能[35]。叶酸参与了调控S-腺苷甲硫氨酸依赖的DNA甲基化过程。缺乏叶酸会导致:①甲硫氨酸合成酶功能下降[36]。②Hcy蓄积[37]。③DNA修复与基因表达失调,加速神经元凋亡[38]。总之,叶酸参与Hcy的再甲基化代谢,其缺乏会导致Hcy蓄积和DNA甲基化异常,影响神经可塑性和突触功能[39]。延缓缺血性卒中后功能恢复,并增加复发概率[40]。

4.3　Hcy与叶酸比值的临床价值

单纯检测Hcy或叶酸可能会受到个体差异的干扰[41]。而Hcy与叶酸的比值更能反映整体代谢失衡状态[42]。该比值升高提示叶酸相对不足或Hcy清除能力下降,这可能加剧血管损伤和神经递质紊乱[43]。亚甲基四氢叶酸还原酶是调节叶酸和Hcy代谢的关键酶[44]。青年缺血性卒中患者常合并*MTHFR*基因突变(如C677T多态性),导致叶酸利用障碍和Hcy代谢受阻[45]。叶酸水平不足会显著放大Hcy的致病效应,进一步增加缺血性卒中复发风险[46]。

5　新型生物分子学标志物

5.1　外泌体微小RNA谱

心脏黏液瘤作为成人最常见的原发性心脏肿瘤,是青年缺血性卒中的重要病因之一[47]。在一项心脏黏液瘤相关缺血性卒中患者的研究中,通过分析血浆和肿瘤来源外泌体中的长链非编码RNA、微小RNA(microRNA, miRNA)和信使RNA表达谱发现,在心脏黏液瘤相关缺血性卒中患者中,可鉴定出5 533个长链非编码RNA和1 331个已知miRNA(另有412个新miRNA);与非缺血性卒中黏液瘤患者相比,检测到差异表达的RNA分子[47]。青年缺血性卒中患者血清外泌体携带独特的miRNA谱,例如hsa-miR-15b-5p、hsa-miR-184和hsa-miR-16-5p在缺血性卒中患者中显著上调,可能通过调控免疫细胞浸润影响缺血性卒中进展[48]。此外,巨噬细胞来源的外泌体miR-30c-2-3p通过促进动脉粥样硬化斑块炎症反应参与大动脉型缺血性卒中,可能靶向动脉粥样硬化相关基因影响斑块不稳定性,进而增加复发风险[49]。另外,大动脉粥样硬化相关的缺血性卒中患者血浆中外泌体miRNA Novel-3特异性上调,可能调控巨噬细胞泡沫化进程加剧动脉粥样硬化发展,成为缺血性卒中复发的潜在驱动因子[50]。这些miRNA谱变化不仅为早期诊断提供分子标志物,同时揭示了免疫调节和血管损伤的核心机制[49]。

5.2　蛋白质组学相关指标

钙结合蛋白是通过激活晚期糖基化终末产物受体通路,诱导血管内皮细胞黏附分子表达,促进单核细胞浸润及斑块不稳定[51]。另外,载脂蛋白C3通过抑制脂蛋白脂肪酶活性,延缓甘油三酯脂蛋白清除,导致甘油三酯升高和脂蛋白残留颗粒积累,促进斑块形成和破裂[52]。在青年人群中,肥胖和胰岛素抵抗的高患病率使载脂蛋白C3驱动的脂毒性及钙结合蛋白介导的炎症反应协同作用,形成促栓性微环境[53]。两者联合效应表现为:①钙结合蛋白诱导的炎症上调载脂蛋白C3表达,而载脂蛋白C3进一步激活钙结合蛋白/晚期糖基化终末产物受体轴,加剧内皮功能障碍和血栓形成[52]。②中性粒细胞胞外陷阱与血小板活化的交叉调控:钙结合蛋白和载脂蛋白C3均可促进中性粒细胞胞外陷阱释放,中性粒细胞胞外陷阱中的组蛋白和髓过氧化物酶进一步激活血小板,抑制天然抗凝系统,导致高凝状态[54]。③代谢-免疫轴失衡:载脂蛋白C3诱导巨噬细胞向促炎M1表型极化,钙结合蛋白抑制调节性T细胞功能,导致免疫失衡和慢性炎症,增加缺血性卒中复发风险[53]。

综上,在青年人群中,钙结合蛋白和载脂蛋白C3通

过协同促进炎症-血栓恶性循环、中性粒细胞胞外陷阱介导的高凝状态及代谢-免疫轴失衡,加速动脉粥样硬化斑块不稳定性,显著增加发生缺血性卒中及复发风险。

6　小结与展望

近年来,预测青年缺血性卒中复发风险的血清学生物标志物研究取得重要突破。现有证据表明,以神经元损伤标志物(如NfL、GFAP)、炎症因子(如IL-6、sCD40L)、凝血功能相关分子(如D-二聚体、纤维蛋白原)及代谢组学标志物(如Hcy、叶酸)为核心的血清指标体系,可通过量化血管内皮损伤、血栓形成倾向以及脑组织继发性损害程度,实现对缺血性卒中复发的早期预警。值得关注的是,基于外泌体miRNA谱和蛋白质组学(如钙结合蛋白、载脂蛋白C3)的新型生物标志物,进一步揭示了神经炎症-血栓形成-代谢紊乱的调控网络,为精准预测模型构建提供了分子生物学基础。

然而,该领域仍面临关键科学问题,比如方法学局限,现有研究多采用单中心观察性设计,样本量普遍不足,且缺乏跨种族和地域的队列验证,限制了研究结果的普适性。同时,标志物联合预测模型多停留于理论验证阶段,动态监测体系因标准化时间窗与阈值界定缺失,难以实现临床转化。

随着生物信息学与人工智能技术的深度融合,未来研究需依托多组学整合分析技术,结合机器学习算法优化动态预测模型,最终建立"筛查-预警-干预"的三级防治体系,以期降低青年缺血性卒中致残性复发带来的社会经济负担。

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