

炎症标志物与卒中后抑郁的相关性研究进展

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摘要

卒中后抑郁(post-stroke depression, PSD)是脑卒中后常见的可治疗的并发症之一, 影响卒中后患者神经功能的恢复和回归社会的能力。免疫反应和炎症反应在PSD的发病机制中起重要作用。本文通过归纳与总结炎性反应参与PSD的发病机制、炎症标志物与PSD的相关性, 为PSD患者的诊断和治疗提供新思路。

关键词

卒中后抑郁, 炎症因子, 发病机制, 生物标志物

Advances in the Study of the Relationship between Inflammation Markers and Post-Stroke Depression

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Abstract

Post-stroke depression (PSD) is one of the common and treatable complications after stroke, affecting the recovery of neurological function and the ability to return to society. Immune response and inflammatory response play important roles in the pathogenesis of PSD. In this paper, we summarize the pathogenesis of inflammatory response involved in PSD and the correlation between inflammatory markers and PSD, so as to provide new ideas for the diagnosis and treatment of PSD patients.

Keywords

Post-Stroke Depression, Inflammatory Factors, Pathogenesis, Biomarker

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1. 引言

卒中后抑郁(post-stroke depression, PSD)是一种卒中患者常见的情绪障碍,主要表现为持续的情绪低落和兴趣缺失,常常伴有躯体症状[1]。研究发现 PSD 发病率高达 27% [2], PSD 不仅影响卒中患者的神经功能、认知功能的恢复,还可导致脑卒中复发、增加自杀风险,严重影响患者的预后。

神经炎症反应参与 PSD 发生、发展的病理及生理过程。新近研究发现,全身免疫炎症指数(systematic immune-inflammation index, SII)、全身炎症反应指数(systemic inflammation response index, SIRI)、中性粒细胞与淋巴细胞的比值(NLR)、血小板与淋巴细胞的比率(PLR)、单核细胞/淋巴细胞比值(MLR)、C 反应蛋白(CRP)、白细胞介素(IL)、肿瘤坏死因子 α (TNF- α)、纤维蛋白原(FIB)等炎症标志物可反映卒中患者的炎症状态,可能对 PSD 的早期诊断、预后预测具有一定的价值[3] [4]。本文通过归纳与总结炎性反应参与卒中后抑郁的发病机制、炎症标志物与 PSD 的相关性,旨在为 PSD 的诊断和治疗提供新思路。

2. 炎症反应与卒中后抑郁

研究发现, PSD 的影响因素主要有年龄、性别、文化程度、家庭年收入、睡眠障碍、既往抑郁史以及脑卒中解剖位置、神经功能缺损程度等,其发病机制尚不明确,目前发现的机制有神经递质系统间的相互调控、神经炎症、神经内分泌激活、神经元可塑性、血管因素[1]。其中,卒中发生后,炎症反应被激活,释放的炎症因子可影响边缘系统下丘脑-垂体-肾上腺(HPA)轴,造成 5-羟色胺(5-HT)和去甲肾上腺素(NE)等神经递质的异常分泌,最终导致 PSD [5]。

2.1. 卒中后小胶质细胞激活引起炎症反应

小胶质细胞(microglia, MG)是一种重要的免疫细胞。脑缺血后, MG 是第一个启动抗原识别、吞噬及呈递的细胞[6]。在正常状态下, MG 是通过感受外界环境的改变而接受神经突触信号,但在外界微环境改变时,其活化和表型改变,并分泌大量的炎症因子[7],同时也能分泌如多巴胺、5-HT 等神经递质。MG 活化后可分为 M1 型和 M2 型。MG 向 M1 型极化,释放促炎因子,导致神经损伤,影响神经网络功能,加剧炎性反应。M2 型 MG 在维持机体稳态中发挥重要作用[8]。在抑郁病人的尸体解剖中发现,大脑前

额叶、前扣带回内的 MG 均有活化。PSD 与 MG 释放的炎症因子密切相关。目前已知的多种抗抑郁药物可抑制 MG 向 M1 型极化。广泛应用于临床的氟西汀、西酞普兰等药物,可调控 MG 的炎性反应,从而影响抗抑郁药物的疗效[9]。进一步验证 PSD 与炎性反应之间的关系。

2.2. 炎症因子影响边缘系统下丘脑-垂体-肾上腺(HPA)轴

已有的研究表明,脑干内有丰富的与情感调控密切相关的甲肾上腺素能和 5-羟色胺能神经元,其轴突经过下丘脑、基底神经节和胼胝体,最终到达额叶皮质。5-HT 和 NE 与焦虑-抑郁、自伤自杀行为和睡眠紊乱等有关。脑卒中后,脑内 NE 和 5-HT 水平降低,会导致抑郁发病风险增加[10]。已有文献报道,PSD 患者脑脊液中 5-HT 的含量降低[11]。抗抑郁药物例如结合选择性血清素再摄取抑制剂(SSRIs)对于 PSD 的治疗效果也表明,NE 和 5-HT 等多种神经递质含量降低,是 PSD 发病的重要原因[12]。

研究表明,炎症反应可通过调控 HPA 轴的功能,减少单胺类神经递质的合成,导致抑郁[13]。脑卒中后,损伤神经元释放的促炎细胞因子可活化 HPA 轴,使皮质醇的分泌增多,进而对神经细胞造成损伤。前期研究发现 PSD 大鼠海马区 TNF- α 、白细胞介素-1 β 和皮质醇释放因子表达增高,且与 TNF- α 信号通路存在交互作用[14]。HPA 轴及下丘脑-垂体-甲状腺轴(PHT)活性异常,可导致血浆皮质醇水平增高,导致肝内色氨酸吡咯酶及氨基转移酶增多,大量产生的酶会降解血液中的色氨酸(5-HT 前体)和酪氨酸(NE 前体),导致 5-HT 和 NE 的合成下降,加重 PSD 发病[15]-[17]。慢性皮质醇增加在脑卒中模型中的持续高水平表达可引起海马神经元再生障碍,进而影响 PSD 的发生。

3. 炎症标志物与 PSD

3.1. 全身免疫炎症指数

全身免疫炎症指数(SII)由 Hu 等人于 2014 年首次提出[18],简单易获得,可综合反应机体免疫与炎症反应之间的关系,计算公式为血小板计数 $\times$ 中性粒细胞计数/淋巴细胞计数。Hou 的研究显示,SII 与急性缺血性卒中的严重程度有关,较 NLR 和 PLR 等指标更具科学性和有效性[19]。近年来,国内外学者对其与抑郁的关系进行了大量的研究,Mazza MG 发现 SII 与新冠肺炎病人的抑郁症、焦虑症有密切关系[20]。Li 等人的研究显示每增加 100 个单位的 SII,抑郁症发生风险提高了 2% [21],提示了 SII 可能是抑郁症中可监测的低级别炎症标志物。Hu 等人对 432 例缺血性脑卒中后 1 个月内的患者进行了随访,其中 129 人在卒中后 1 个月内确诊 PSD,研究发现 SII 水平增高是 PSD 发病的独立危险因素,特别是住院时的 SII 水平增高,与 PSD 显著相关,有可能成为 PSD 的预后指标[22]。

3.2. 全身炎症反应指数

全身炎症反应指数(SIRI)由 Qi 等人于 2016 年首次提出,是一种具有较高临床应用前景的炎症生物学标志物[23]。SIRI 可以预测多种严重疾病的预后,如结直肠癌、胆囊癌、高血压和心力衰竭等[24]-[27],计算公式为中性粒细胞计数 $\times$ 单核细胞计数/淋巴细胞计数。Chu M 等人的研究显示 SIRI 是卒中后认知功能损害的一个独立危险因素[28]。黄小妹等人[29]研究发现 SIRI 升高,发生 PSD 的风险增加, $SIRI \geq 1.5 \times 10^9$ 是 PSD 的独立危险因素。目前关于 SIRI 与 PSD 相关性的研究较少,未来还需要进一步探讨。

3.3. PLR、NLR、MLR

近年来,中性粒细胞与淋巴细胞的比值(NLR)和血小板与淋巴细胞的比值(PLR)已成为评估机体炎症状态的公认生物标志物。NLR 和 PLR 是简单、经济的生物标志物,在常规检查中可以很容易地从血液中提取出来[30]。单核细胞/淋巴细胞比值(MLR)是近年来备受关注的新型炎症指标,其反映了外周血中单核细胞与淋巴细胞之间的动态平衡,也可直接反映机体炎症状态。卒中后外周血中立即诱导中性粒细胞和

单核细胞的上调以及淋巴细胞的减少,它们被炎症介质吸引,并通过受损的血脑屏障募集并浸润到大脑,这极大地促进了 PSD 的发生和发展。

NLR 及 PLR 均与多种精神类疾病有关,且与抑郁症为主[31]。NLR 及 PLR 升高与重度抑郁症发生风险增加密切相关[32][33]。近年来的研究表明,NLR、PLR 与脑梗死患者的预后密切相关[34]。卒中后,包括中性粒细胞在内的免疫细胞穿过受损的血脑屏障向坏死区域迁移,并分泌大量的炎症介质和促炎因子[35],激活机体免疫系统,产生免疫级联放大反应,进而导致细胞功能障碍和氧化应激[36]。炎症状态可改变颅内神经内分泌功能,同时降低单胺类神经递质的合成和分泌,导致卒中后抑郁的发生[37]。另一方面,淋巴细胞的减少反映了机体处于病理应激状态,预示着较差的预后[38]。因此,NLR 既能反映脑卒中后的炎性状态,又能反映卒中后抑郁状态的发生发展,对卒中后抑郁有一定的预测价值。

血小板是一种反映炎症状态的特异性生物标记物,其激活与抑郁症等精神疾病有关,是一种明确的危险因素[39]。脑卒中后,坏死区释放大炎症介质,促进巨噬细胞的活化,进而激活血小板,活化的血小板可通过分泌炎症因子调节内皮细胞通透性,募集单核细胞[40],促进炎症反应。同时,活化的血小板释放 5-HT,而 5-HT 在抑郁症的形成过程中起重要作用。另一方面,促炎因子也由激活的血小板产生,并参与了炎症反应的启动、维持及调控,在抑郁的发生发展中发挥了关键作用。此外还有学者发现,促炎因子、活化血小板可能通过抑制脑源性神经营养因子(BDNF)和 BDNF 受体(TrkB)磷酸化表达,导致抑郁发生[41]。因此,我们推测卒中后血小板激活与炎症反应及 PSD 的发生之间存在交互作用,PLR 或许可以作为预测 PSD 的可靠指标。

Hu 等人通过使用逻辑回归分析发现,NLR(≥ 4.02)和 PLR(≥ 203.74)与 PSD 独立相关,且较高的 NLR 和 PLR 与卒中后 6 个月的抑郁症有关,在 PSD 的早期临床检测中,综合指数比单独使用更有意义[42]。Cheng 等人通过元回归分析发现在中国亚组和匹配的年龄和性别中,患有 PSD 的个体具有更高的 NLR 和 MLR 值[43]。Huang 等人研究发现入院时 PLR 增加是预测 PSD 发展的独立生物标志物,分层 PLR 可以提高对 PSD 患者的预测能力[44]。综上所述,PLR、NLR、MLR 或许可作为预测 PSD 患病及严重程度的血液学参考指标[45]。

3.4. 白细胞介素

白细胞介素(IL)是一类具有多种生物学特性的细胞因子,包括 IL-1 β 、IL-6、IL-8、IL-10、IL-18 等,主要参与信息传递、免疫调节、炎症调控,当中枢神经系统受到损伤或感染后,IL 水平明显升高。炎症因子(促炎细胞因子、抗炎细胞因子等)在 PSD 发生发展中起重要作用[46]。Wang 的研究表明患者血液中 IL-6 水平显著升高与 PSD 发生密切相关。生物标志物的检测可以有效预测 PSD 的发生,具有较高的临床价值[47]。Korostynski 等人在研究中发现卒中后 3 个月出现抑郁症状的患者血浆 IL-6 水平高于 TNF- α 、sIL-6R 和 IL-1 α 。血浆 IL-6 可预测卒中后 3 个月时抑郁症状的严重程度,还可能与卒中后 3 个月出现的抑郁症状有关[48]。Yi 等人的研究表明 IL-1 β 与中风后 6 个月的 PSD 密切相关,高 IL-1 β 是 PSD 发展的独立危险因素[49]。杨等人的研究发现,IL-18、IL-1、IL-6 在 PSD 发生、发展和转归密切相关[50]。Kim 等人研究了 PSD 患者的促炎细胞因子基因如 IL-1 β 、IL-6、IL-8、TNF- α 的多态性以及抗炎细胞因子如 IL-4 和 IL-10 的多态性,并检测其与抑郁发生发展的关系,发现 IL-10-1082A/A 基因型与 PSD 关系密切,而 IL-4+33C/C 基因型只与重度 PSD 有明显的相关性[51]。通过对 PSD 患者一年的追踪研究,Su 等人发现抑郁组组的 IL-10 含量明显降低,且与抑郁程度呈负相关。提示 IL-10 可能具有潜在的抗抑郁效应[52]。这些研究将为阐明 PSD 的发病机制提供新的理论依据。

3.5. C 反应蛋白

C-反应蛋白(CRP)作为一种高度敏感的急性期蛋白,不仅可以反映脑卒中神经损伤的程度,还可以反

映大脑的微炎症,被认为可以预测急性脑卒中患者的疲劳、认知障碍[53]、死亡风险和长期康复。PSD 不但与脑损伤后的神经功能缺损症状有关,还与患者的心理反应机制有关[54]。一些研究表明,即使在轻度卒中的患者中,PSD 也经常发生[55]。因此,可以根据 CRP 水平和脑卒中的严重程度来预测 PSD 的发生。研究发现 NIHSS 评分、CRP、NLR 是 PSD 发生的独立危险因素,NLR 联合 CRP 预测 PSD 的敏感性 & 特异性较高,具有更高的预测价值[56]。此外,脑卒中急性期的同型半胱氨酸联合 CRP 也可以预测 PSD 的发生[57]。同时一项荟萃分析的结果再次证实了这一结论,PSD 对卒中患者的生存率有负面影响[58]。因此,脑卒中急性期 CRP 升高也表明患者预后不良的可能性[59]。目前的研究只是揭示了 CRP 与 PSD 发作的临床相关性,但 PSD 患者伴有血管性病变(如大脑动脉粥样硬化等),PSD 患者发生抑郁的介导环路与普通抑郁患者可能存在区别。PSD 的发生与脑内奖赏环路的关系以及 CRP 在 PSD 中的作用机制尚不清楚。

3.6. 肿瘤坏死因子 α

中枢神经细胞、星形胶质细胞及小胶质细胞等受外界因素的影响,可分泌 TNF- α ,从而影响细胞的信号传导、转录、促炎和凋亡等。通过 Logistic 回归分析,发现 TNF- α 为 PSD 的独立危险因素,TNF- α 表达水平对于 PSD 的治疗和预防极为重要[60]。一项关于探讨慢性不可预测轻度应激源(CUMS)下大脑中动脉闭塞后抑郁大鼠的下丘脑-垂体-肾上腺轴(HPAA)活性及细胞因子变化的研究,发现 TNF- α 及其信号通路 STAT3/SOCS3 在 mRNA 和蛋白质中水平上调,提供了支持缺血性卒中和 CUMS 后促肾上腺皮质激素释放因子系统和 TNF- α 信号通路之间信号串扰假说的证据[14]。Reichenberg 等人的研究显示,TNF- α 可引起抑郁症和认知功能障碍[61]。以上研究提示升高的 TNF- α 可能从神经突触受体、可塑性及递质降解等途径介导慢性应激诱导抑郁样行为,在 PSD 病理生理学机制中发挥着协同作用,是 PSD 干预的重要潜在靶点。

3.7. 纤维蛋白原

纤维蛋白原(FIB)是一种重要的凝血因子和炎症因子。相关研究表明 FIB 水平与卒中发生风险密切相关[62]。较高的血栓负荷与更严重的卒中症状和不良预后有关[63]。此外,高水平的 FIB 可能导致心理困扰。Marie 等人对 73,367 名普通人群进行了一项研究,发现 FIB 与抑郁症呈正相关[64]。在早期高 PSD 风险患者中,血浆 FIB 升高增加了发生持续性 PSD 的风险[65]。Zhu 等人的研究表明女性、基线卒中严重程度和较高水平的 FIB 与出院时 PSD 独立相关[66]。FIB 还与汉密尔顿抑郁量表 17 项(HAMD-17)评分呈正相关[67]。FIB 可能是缺血性卒中患者发生 PSD 的独立预测因子。此外,FIB 和中性粒细胞计数的链介导作用可能在 PSD 的发生中起重要作用[68]。现阶段研究中,关于 FIB 与 PSD 相关的基础研究几乎处于空白。FIB 如何在 PSD 病理生理学机制中发挥作用,需要进一步研究。

4. 小结

PSD 的发病机制多种多样,炎症在其发生和发展中起着至关重要的作用。炎症反应与其他机制并非相互独立,而是错综复杂的相互关联。近年来国内外较多学者发现炎症相关标志物能够评估 PSD 状态下机体的炎症情况,是早期诊断 PSD 和预测 PSD 预后的重要生物学指标。目前关于 PSD 和炎症标志物的相关性研究有限,亟需更多大样本、多中心的研究,以验证两者之间的关系,并进一步比较不同炎症标志物对 PSD 的预测价值,以期 PSD 患者提供科学、实用、高效的评估方法,也为临床医护人员做出正确临床决策提供参考,早期诊断 PSD,给予有效干预,改善患者预后。

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