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卒中后抑郁的机制、危险因素以及评估的相关研究进展

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摘　要

卒中后抑郁(post stroke depression, PSD)是缺血性卒中常见和严重的后遗症之一，是一种多因素导致的神经精神病学表现。目前认为PSD成为了卒中后幸存患者恢复不良、生活质量不佳、功能能力差和康复效果不佳的主要驱动因素，本文对PSD的机制、危险因素以及评估的最新研究进展进行综述，以期为PSD的预测、诊断、治疗的深入研究提供参考信息。

关键词

卒中后抑郁，机制，危险因素，评估

Research Progress on the Mechanism, Risk Factors and Evaluation of Post-Stroke Depression

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Abstract

Post stroke depression (PSD) is one of the common and serious sequelaes of ischemic stroke, and is a multifactorial neuropsychiatric manifestation. Currently, PSD is considered to be the main driving factor of poor recovery, poor quality of life, poor functional ability and poor rehabilitation

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effect in surviving patients after stroke. This paper reviewed the latest research progress on the mechanism, risk factors and evaluation of PSD, in order to provide reference for the prediction, diagnosis and treatment of PSD.

Keywords

Post-Stroke Depression, Mechanism, Risk Factors, Assessment

1. 卒中后抑郁

卒中后抑郁是指发生于卒中后，出现卒中症状以外的一些以兴趣丧失、情绪低落为核心，以情感障碍为主要临床表现的综合征，常伴发焦虑或躯体化的症状。PSD 导致患者有较高的复发率、死亡率以及减少治疗、恢复的有效率。现每年世界脑卒中的人数在增加，PSD 患者总数呈直线上升趋势，PSD 的在卒中患者发病率大约在 33.5% [1] [2]。因此，重视卒中患者的情感障碍情况，给予及早有效的防治措施，是改善其功能恢复及预后生存的重要方式。现阶段，PSD 的发病机制并不明确，其治疗方案也多种多样。许多因素导致 PSD 的发生，所以充分认知 PSD 的机制、危险因素和评估方法对于其诊断、治疗十分有利。

2. PSD 的机制

根据现有的研究来看，对于解释 PSD 的机制还没有一个统一的理论。更好地了解 PSD 的病理生理机制有助于患者对 PSD 进行靶向治疗。本文简述最新研究 PSD 的主要病理生理机制如下。

2.1. 营养因子与遗传基因

PSD 是多因素疾病，营养因子和遗传基因可能参与其发病机制，但 PSD 的遗传基础鲜为人知。目前较多的研究表明，脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)的释放可促进血清张力能轴突的存活和萌发，增强 5-HT 摄取和活性依赖性释放，在 PSD 患者中，他们的血清 BNDF 水平低于那些没有抑郁症的患者[3]。此外，抗抑郁药可以增强大脑中的 BDNF 表达，从而缓解抑郁症状。这种治疗效果可以在删除 BDNF 基因的动物中废除[4]。赵富英等人在有针对性的中风患者有或没有抑郁症患者的定向测序中发现了 HTR3D 和神经 G3 与中国汉族人口中风的 PSD 和 PIK3C2B 的易感性有关[5]。梁金凤的研究证明 TrkB 基因、BDNF 和 TrkB 单体型以及 p11、tPA 和 BDNF 之间的基因相互作用都与 PSD 有关，这表明 p11/tPA/BDNF 通路中的基因变异在调节 PSD 的基本机制方面可能发挥核心作用[6]。也有研究发现神经营养酪氨酸激酶受体 B (TrkB)基因中通过高分辨率熔化分析进行的三种单核苷酸多态性(SNPs)，即 rs1187323、rs1212171 和 rs1778929，结果是 rs1778929 (P = 0.024)的次要等位基因(T)，OR = 0.725，95% CI = 0.590~0.890)和 rs1187323 (P = 0.000, OR = 0.598, 95% CI = 0.466~0.767)的次要等位基因 C)被发现与 PSD 有显著关联[7]。

2.2. 细胞因子失调

近年来越来越多的研究表明，炎症反应与 PSD 有着密切的关系，卒中是一种脑组织的损伤，可引发

强烈的炎症反应，促炎细胞因子由受损的神经元释放出来，激活小胶质细胞，炎症进而蔓延至偏远地区，诱发 PSD 的发生[8]。促炎细胞因子可以刺激基质金属蛋白酶的产生，然后通过内皮细胞迁移去破坏血脑屏障，或者通过诱导糖皮质激素抵抗的机制来影响着 PSD [9] [10]。常见的促炎细胞因子有白细胞介素-6 (IL-6)、肿瘤坏死因子-α (TNF-α)、白细胞介素-1 (IL-1+)、C 反应蛋白(CRP)、白细胞介素-33 (IL-33)、系统免疫炎症指数(SII)、中性粒细胞对淋巴细胞(NLR)、血小板对淋巴细胞(PLR)和衍生中性粒细胞与淋巴细胞比率(dNLR)、单细胞与淋巴细胞比(MLR)、可诱导的一氧化氮合成酶(iNOS)和巨噬细胞炎症蛋白 1+ (MIP-1+)，以上促炎因子都已频繁被研究分析后得出结论：在 PSD 患者中可检测到较非 PSD 卒中患者高[11]-[16]。同时，最近一项研究表明抗炎因子白细胞介素-10 (IL-10)与 PSD 呈负相关，这也反向证明了促炎细胞因子的升高诱导了 PSD 的发生[17]。恩·卡佩尔曼的临床研究分析得出结论对 PSD 患者进行抗细胞因子治疗具有显著的抗抑郁作用[18]。同型半胱氨酸(HCY)增加也会导致 PSD 的风险升高[19]。虽然以上促炎细胞因子与 PSD 发病机制存在一定的联系，但它们还不是 PSD 最佳反应因子，这也突出了对更特定生物标志物的需求。

2.3. 神经递质紊乱

目前关于 PSD 的神经递质的理论主要有单胺能假说和谷氨酸介导的兴奋毒性假说。患者发生缺血性脑卒中(cerebral ischemic stroke, CIS)后，大脑的 5-羟色胺(5-HT)、去甲肾上腺素(NE)和多巴胺(DA)的相关传导通路受到了一定影响，5-HT 受体无法上调导致 5-HT 合成不断减少，促进抑郁的发生[20]。扎哈尔等[21]研究显示，PSD 组小鼠卒中部位(左侧扣带回)和左侧大脑白质的 5-HT、NE 神经分布相对于对照组明显减少。而对其使用选择性 5-HT 再摄取抑制剂能有效提高 5-HT 水平，改善抑郁症状。研究人员还发现 5-HT、NE 和 DA 神经元在中枢神经系统(central nervous system, CNS)中直接或间接存在相互作用[22]。另外，最近很多人研究谷氨酸学说，谷氨酸是一种非必需氨基酸，中风期间，脑外液和脑脊液(cerebrospinal fluid, CSF)中的谷氨酸浓度增加 300~400 倍，约占所有神经介质活动的 60%。急性 CIS 后，大脑谷氨酸水平升高和扩散，造成梗死组织以外区域的神经元损伤，过量的谷氨酸刺激谷氨酸受体，导致细胞肿胀、凋亡和神经元死亡，随后神经功能不良。谷氨酸水平会导致抑郁、焦虑、痴呆和其他精神疾病，PSD 患者的脑谷氨酸水平升高[23]。此外，有研究发现炎症因子对中央谷氨酸有促进作用[24]。因此，本文推测，卒中导致神经递质，特别是 5-HT 和谷氨酸的改变，触发 PSD。

2.4. 下丘脑－垂体－肾上腺轴异常

下丘脑－垂体－肾上腺轴(hypothalamic-pituitary-adrenal, HPA)是主要的神经内分泌应激反应系统，涉及代谢、免疫和调节情绪。当患者发生卒中后，下丘脑接收到来自海马或其他组织的信号时，下丘脑室旁核释放促肾上腺皮质激素释放激素(corticotropin releasing hormone, CRH)，CRH 刺激垂体释放促肾上腺皮质激素(adrenocorticotrophic hormone, ACTH)，ACTH 作用于肾上腺皮质合成和释放糖皮质激素，糖皮质激素也可以反向通过海马、下丘脑和垂体对 HPA 轴进行负调控[25]。当 HPA 轴过度活化时，可进一步导致下丘脑内源性大麻素 CB1 受体水平的异常，与 PSD 的形成有着重要的关联。HPA 轴刺激皮质醇增多，高皮质醇症与 PSD 也有很大关系[26]。然后也有研究得出促炎细胞因子刺激下丘脑－垂体－肾上腺轴释放糖皮质激素，这种慢性炎症刺激可导致 HPA 轴的失调，进而 ACTH 与皮质醇水平的上调，导致神经系统疾病的恶化，而高水平的皮质醇可引起炎症反应的加剧。此外，HPA 轴还通过影响 5-HT 与 5-HTTLPR 的结合(以及其他单胺与其转运体的结合)与 5-HT 系统相关，而 5-HTTLPR 多态性通过影响皮质醇的水平进而刺激 HPA 轴[27]。由此可以发现 HPA 轴、5-HT 系统以及炎性因子都是相互作用在 PSD 的发病机制中。

2.5. 肠道菌群紊乱

近年来肠道菌群是 PSD 的机制最新研究的关注点，在很多疾病的机制中都存在一个肠脑轴(gut-brain axis, GBA)即肠道和微生物区系、中枢神经系统之间的一个复杂的双向通信网络，很多研究证实 PSD 与 GBA 有一定的关系。在范文涛的研究中发现，PSD 患者的肠道多样性指数香农维纳指数(Shannon)，辛普森指数(Simpion)均高于对照组，致病菌肠杆菌数量相比正常也增加，同时益生菌数量比例减少[28]。其中的机制，一方面可能是，卒中的发生可以改变患者的肠道微生物群、破坏肠道的完整性，进而导致肠道通透性增加、营养不良，使得肠腔向血液循环中释放细菌和毒素，刺激全身炎性因子产生和释放，从而加重卒中损害程度及卒中后并发症的发生[29]。另一方面为，科林发现肠道菌群失调可通过改变 T 细胞内稳态，诱导促炎症反应和氧化应激，加剧小鼠的脑损伤[30]。而且也有研究证明，在抑郁症患者中服用益生菌相比于安慰剂来说更能够改善抑郁症状，益生菌对脑组织具有保护作用[31]。由此可见，肠道菌群的紊乱，使得大脑和肠道之间的信息通路发生障碍，可能是 PSD 发生的一个病理机制，未来进一步对肠道菌群研究可能是获得 PSD 治疗的新方法。

3. PSD 的危险因素

PSD 的危险因素有很多，掌握其可以助我们在临床上早期预防卒中患者 PSD 的发生和进一步探讨其可能发生的机制。本文总结了以下危险因素，但其中一些危险因素仍存在争议，需要进一步研究。最常见的危险因素是卒中严重程度、认知障碍、身体残疾、功能依赖、卒中位置(大脑左侧)、年龄、较长的高血压史[32] [33]。另外，Dong L 的研究表明中风前的睡眠时间短可能是中风后抑郁症的一个独立危险因素[34]。佩兰 R 通过 Meta 分析独立提取数据，得出了女性性别是一个独立危险因素[35]。涂宣强的研究卒中后男性患者的垂直白质超强(PVWMH)可能与 PSD 发生存在一定的关系，但性别可能在 PSD 发生的时间上有一定的影响[36]。另外，后屋搜索了 MEDLINE、精神病学、EMBASE 等数据进行统计分析出了中风后抑郁症患者受教育年数少于无中风后抑郁症患者(MD 0.68 95% CI 0.05~1.31 p = 0.04) [37]。还有严重牙周炎、失语症、脑动脉狭窄、以往的抑郁症史也是急性缺血性中风患者早期发作 PSD 状态的重要独立预测因素[38] [39] [40]。当患者发生卒中时，医护人员可以从以上方面警惕 PSD 的发生，及时准确选择对应的干预措施和治疗方案。

4. PSD 的评估方法

虽然 PSD 在卒中后发病率约占三分之一，但是及时检测出中风后抑郁症却比较少[41]，而且最佳筛查问卷尚未确定，所以了解 PSD 的最佳评估量表十分必要。目前临床医生和研究者广泛使用汉密尔顿抑郁评定量表(Hamilton Depression Rating Scale, HDRS)，因为它已多次被证明在测量中风患者抑郁症状方面具有可靠性和有效性[42]患者健康问卷-9 (PHQ-9)由九个问题组成，完成时间不到 5 分钟，它的灵敏度和特异性都比较高，可用于检测中风后患者的主要抑郁症的工具[43]。乔伊 C 普利斯尼研究表明，与 PHQ-2、医院焦虑、抑郁量表(HADS-D)和老年抑郁症量表(GDS-15)进行对比，得出了 PHQ-9 (灵敏度：81.8%，特异性：97.1%)，PHQ-2 (灵敏度：75.0%，特异性：96.3%)、HADS-D (灵敏度：63.6%、特异性：98.1%)和 GDS-15 (敏感性：45.5%，特异性：84.8%)，PHQ-9 是这四个量表中最合适的抑郁症筛查工具[44]。另外迈克尔收集了的临床试验数据集进行二次数据分析，将 CESD-10 与 CESD-20 予以比较，得出了 CESD-10 与 CESD-20 高度相关，而 CESD-10 具有更好的可靠性、有效性，是衡量中风后个人抑郁症的有效指标[45]。以上的 PSD 的评估量表可以为我们临床所用，为了诊断的准确性，我们建议这些筛查工具应联合使用。未来对 PSD 的评估量表进一步研究十分有必要。

5. 总结

当今社会随着卒中发病率的增加，PSD 也随之增加，PSD 与卒中可以相互影响，导致卒中具有高复发率及病死率，但目前研究的其危险因素还在进一步完善、病理生理学机制也不够明确。研究其具有代表性的检测指标和更明确其发病机制对 PSD 的早期识别和正确治疗至关重要，如果不及早识别和采取适当的干预措施，抑郁症状就会持续缓慢发展，给患者及家庭带来更糟糕的后果，未来还需对 PSD 的临床研究进一步探索。

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