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卒中后癫痫研究进展：病理生理、诊断、治疗与预后

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摘　要

卒中后癫痫(PSE)是卒中患者常见的严重并发症，显著影响其预后与生活质量。本文系统综述PSE的病理生理机制、诊断技术、治疗策略及预后因素的研究进展。病理生理方面，重点探讨脑损伤后神经递质失衡、离子通道异常、血脑屏障破坏及炎症反应的交互作用；诊断部分，结合脑电图、影像学与血液生物标志物的临床价值与局限性展开分析；治疗策略涵盖抗癫痫药物的选择、神经调控技术的应用及手术干预的适应证；预后部分则从卒中类型、发作特征及治疗依从性等多维度解析影响因素。本文旨在整合现有研究成果，为优化PSE的临床管理及未来的研究方向提供参考。

关键词

卒中后癫痫，病理生理，诊断技术，治疗方法

Research Progress of Post-Stroke Epilepsy: Pathophysiology, Diagnosis, Treatment and Prognosis

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Abstract

Post-stroke epilepsy (PSE) is a common serious complication of stroke patients, which significantly affects their prognosis and quality of life. This article systematically reviews the research progress

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of the pathophysiological mechanism, diagnostic techniques, treatment strategies and prognostic factors of PSE. In terms of pathophysiology, it focuses on the interaction of neurotransmitter imbalance, ion channel abnormalities, blood-brain barrier disruption and inflammatory response after brain injury; in the diagnostic part, the clinical value and limitations of electroencephalography, imaging and blood biomarkers are analyzed; in the treatment strategy, the selection of anti-epileptic drugs, the application of neuroregulatory techniques and the indications of surgical intervention are covered; in the prognosis part, the influencing factors are analyzed from multiple dimensions such as stroke type, seizure characteristics and treatment compliance. The purpose of this paper is to integrate existing research results and provide a reference for optimizing the clinical management of PSE and future research directions.

Keywords

Post-Stroke Epilepsy, Pathophysiology, Diagnostic Techniques, Treatment Methods

1. 引言

卒中是全球范围内导致死亡和残疾的主要原因之一，而卒中后癫痫(post-stroke epilepsy, PSE)作为卒中的常见并发症，其发病率呈逐年上升趋势，严重影响患者的预后和生活质量[1]。卒中是老年人癫痫发作和癫痫的最常见原因[2]。据统计，2%~14%的缺血性卒中幸存者发展为 PSE，10%~20%的出血性卒中幸存者可出现 PSE [3]，在某些特定人群中，这一比例可能更高。PSE 是脑卒中预后的关键决定因素，与高死亡率、预后差和住院时间延长有关[4]。PSE 对患者的认知功能、心理状态和社会功能造成显著损害[5]，加重了医疗负担。

卒中后癫痫发作分为早发性癫痫发作和晚发性癫痫发作。早发性癫痫发作发生在卒中后 7 天内[6]，通常认为由卒中的代谢效应引起。晚发性癫痫发作是卒中 1 周后出现的无端发作。早发性癫痫发作再次出现无端发作的风险约为 30%，而根据 2005 年的癫痫定义“间隔 24 小时的两次无端发作”，早发性癫痫发作因复发风险低而不被认为是癫痫[7]。卒中后的晚发性癫痫发作具有>60%后续无端发作的风险，足以在这种情况下诊断癫痫[8]。PSE 最常见的发作类型是局灶性发作或发展为双侧局灶性发作的强直－阵挛性发作[9]。

因此，深入研究 PSE 的病理生理机制、诊断方法、治疗策略和预后因素具有重要的临床意义。

2. PSE 的病理生理机制

2.1. 神经递质失衡

谷氨酸是中枢神经系统中主要的兴奋性神经递质[10]，在正常生理状态下，其释放与摄取处于动态平衡。卒中发生后，脑局部组织缺氧、缺血，导致神经元能量代谢障碍，细胞膜上的谷氨酸转运体功能受损，谷氨酸摄取减少，同时神经元大量释放谷氨酸[11] [12]。过量的谷氨酸在细胞外积聚，过度激活 N-甲基-D-天冬氨酸(NMDA)受体和 α-氨基-3-羟基-5-甲基-4-异恶唑丙酸(AMPA)受体等兴奋性氨基酸受体，引起神经元持续性去极化，导致细胞内钙离子超载[13]-[16]。钙离子超载进一步激活一系列细胞内酶，如钙蛋白酶、磷脂酶等，引发神经元损伤和死亡，破坏了神经元的正常兴奋性－抑制性平衡[17] [18]，增加

了癫痫发作的易感性。

γ-氨基丁酸(GABA)是中枢神经系统中重要的抑制性神经递质，主要通过与 GABA 受体结合发挥抑制性作用。卒中后，脑内 GABA 能神经元受损，GABA 合成酶活性降低，导致 GABA 合成减少。同时，GABA 的摄取和代谢过程也可能发生紊乱，使得细胞外 GABA 浓度降低，对神经元的抑制作用减弱，从而促进癫痫的发生[19] [20]。

2.2. 离子通道异常

电压门控钠通道在神经元动作电位的产生和传播中起关键作用。卒中可引起神经元细胞膜电位改变，影响钠通道的功能和表达[12]。有研究发现，卒中后钠通道的失活过程可能延迟，导致神经元兴奋性增加。钠通道的异常激活可使神经元在较小的刺激下即可产生动作电位，降低了神经元的兴奋阈值，易于引发癫痫样放电[21]。

钙通道在调节神经元内钙离子浓度方面具有重要作用[22]。卒中后，钙通道的结构和功能可能发生改变，细胞外钙离子通过异常的钙通道大量内流，导致细胞内钙离子超载。这不仅可直接损伤神经元，还可激活钙依赖性信号通路，影响神经元的基因表达和蛋白质合成，进而改变神经元的兴奋性和可塑性，增加癫痫发作的风险[21] [23]。

2.3. 血脑屏障破坏

血脑屏障(blood-brain barrier, BBB)由紧密连接的内皮细胞、基膜、周细胞和星形细胞端足组成，它形成了一个物理屏障，保护中枢神经系统免受细胞旁有害物质流动的影响[15] [24]。卒中导致脑内血管内皮细胞损伤、紧密连接蛋白破坏，引起 BBB 通透性增加[12] [24] [25]。血脑屏障破坏后，血液中的炎性细胞、蛋白质和其他物质可进入脑实质，引发炎症反应。同时，外周的免疫细胞和炎性介质也可通过受损的血脑屏障进入脑内，进一步加重脑内炎症。炎症反应可释放多种炎性细胞因子，如肿瘤坏死因子-α (TNF-α)、白细胞介素-1β (IL-1β)等，这些细胞因子可影响神经元的兴奋性，促进癫痫的发生[25] [26]。此外，血脑屏障破坏还可能导致脑内环境紊乱，影响神经递质的代谢和清除，间接促进癫痫的发生发展[25]。然而，一些学者认为血脑屏障改变是癫痫发作的后果[21]。有研究认为被激活的小胶质细胞分泌的 TNF-α、IL-6 和 IL-1β 会导致 BBB 的破坏[27]。这其中的因果关系需要我们进一步的研究。

2.4. 炎症反应

卒中引发的脑损伤可激活小胶质细胞，使其从静息状态转变为激活状态。激活的小胶质细胞释放大量炎性细胞因子和趋化因子，如 TNF-α、IL-1β、IL-6 等[28]，这些炎性介质可促进神经元的兴奋性，诱导癫痫发作[29] [30]。小胶质细胞还可通过吞噬作用清除受损的神经元和神经胶质细胞，但在过度激活的情况下，可能会对周围正常组织造成损伤，进一步破坏脑内的神经环路和微环境，增加癫痫的发病风险[31] [32]。

星形胶质细胞在维持脑内环境稳定和神经递质代谢方面发挥重要作用。卒中后，星形胶质细胞发生反应性增生和功能改变，其对谷氨酸的摄取和代谢能力下降，导致细胞外谷氨酸浓度升高。同时，星形胶质细胞释放的一些炎性介质也可参与癫痫的发病过程[33]-[35]。此外，星形胶质细胞与神经元之间的相互作用紊乱，影响了神经元的正常功能和兴奋性调节，促进了癫痫的发生[32] [34] [36]。

2.5. 遗传因素

部分卒中后癫痫患者存在遗传易感性。一些基因的突变或多态性可能影响神经递质代谢、离子通道功能等，从而增加了卒中后癫痫的发病风险。有研究发现线粒体醛脱氢酶 2 (ALDH2)基因 rs671 多态性中

rs671 多态性的等位基因 A 可影响血浆 4-羟基壬烯醛水平和脑卒中后癫痫易感性，ALDH2 的过表达可被 4-羟基壬烯醛介导的丙二醛(MDA)和氧自由基的增加部分阻断，随后的神经元凋亡由此降低，降低脑卒中后癫痫发生的概率[37]。另一项系统性评价发现 CD40 等基因的多态性等与卒中后癫痫呈正相关，而 S100 钙结合蛋白 B 等与卒中后癫痫呈负相关，但由于招募的患者数量较少，需要进一步研究来证实[38]。然而，目前关于卒中后癫痫相关遗传因素的研究尚处于初步阶段，具体的遗传机制仍有待进一步深入探索[39]。

3. PSE 的诊断方法

3.1. 脑电图(Electroencephalography, EEG)

脑电图是诊断 PSE 最客观的辅助检查方法，在癫痫发作预测、疾病监测、药物选择、预后评价等方面发挥着非常重要的作用[3]。在急性卒中阶段，脑电图可出现局灶性或弥漫性慢波，提示脑功能受损。随着病情的进展，部分患者可出现癫痫样放电，如棘波、尖波、棘慢波综合等[40]。一些研究表明，卒中后早期脑电图出现癫痫样放电的患者，发生 PSE 的风险较高[40]-[42]。然而，脑电图的敏感性和特异性存在一定的局限性，部分患者在发作间期脑电图可能正常，需要多次检查或进行长程脑电图监测以提高诊断准确性。

3.2. 影像学检查

脑磁共振成像(MRI)和计算机断层扫描(CT)等影像学检查可帮助确定卒中的部位、范围和类型，对 PSE 的诊断具有重要的辅助作用[43]。在 PSE 患者中，MRI 可能显示脑软化灶、海马硬化、脑萎缩等病变[44] [45]，这些病变部位与癫痫发作的起源可能相关。功能磁共振成像(fMRI)可检测脑功能活动的改变[46]，有助于发现潜在的癫痫病灶[47]。但影像学检查结果不能直接确诊 PSE，需要结合临床症状和脑电图等其他检查进行综合判断。

3.3. 血液生物标志物

近年来，一些血液生物标志物在 PSE 的诊断研究中受到关注。例如，神经元特异性烯醇化酶(neuron-specific enolase, NSE)、S100 钙结合蛋白 B (S100 calcium-binding protein B, S100B)等在卒中后脑损伤时可释放到血液中，其水平升高可能与癫痫发作风险相关[48]。Abraira 等人的研究[49]指出，肿瘤坏死因子超家族成员 14 (tumour necrosis factor superfamily 14, TNFSF-14)成为预测 PSE 的潜在生物标志物。然而，目前这些生物标志物的特异性和准确性尚不足以单独用于 PSE 的诊断，仍需进一步研究和验证。

4. PSE 的治疗策略

4.1. 抗癫痫药物(Antiepileptic Drugs, AED)治疗

目前新型抗癫痫药物如左乙拉西坦、拉考沙胺、吡仑帕奈等在 PSE 治疗中的应用逐渐增多[8]。左乙拉西坦通过与突触囊泡蛋白 SV2A 结合，调节神经递质释放，具有良好的耐受性和较少的药物相互作用[50]-[52]。脑卒中后抑郁很常见，有研究指出左乙拉西坦对行为的有害影响可能会进一步加剧精神合并症，提出左乙拉西坦不适合脑卒中后抑郁患者[53]。拉考沙胺作用于电压门控钠通道，可选择性地增强慢失活状态钠通道的稳定性，对部分性发作和难治性癫痫有效[54] [55]。吡仑帕奈是一种选择性 AMPA 受体拮抗剂，可有效减少癫痫发作频率[56] [57]。PSE 患者可能有一定的心血管危险因素负担，因此，应避免使用苯妥英、苯巴比妥等能增加血管疾病生化指标的药物[58]。有临床研究显示，新型抗癫痫药物在控制 PSE 发作方面具有一定优势，且不良反应相对较轻，但仍需更多大规模临床试验进一步验证其疗效和安

全性。

目前的指南缺乏治疗 PSE 的强有力的建议。对于合适的 AED 的决策与其他类型的癫痫相同，应综合考虑患者的年龄、性别、肝肾功能、发作类型、药物不良反应等因素。同时，应密切监测药物不良反应，定期进行血常规、肝肾功能等检查，及时调整治疗方案。值得注意的是，没有 I 类证据支持使用任何抗癫痫药物来预防 PSE 的发生[59]。

4.2. 神经调控治疗

重复经颅磁刺激(repetitive transcranial magnetic stimulation, rTMS)是一种非侵入性的神经调控技术，通过在头皮表面施加磁场，诱导大脑皮质产生感应电流，调节神经元的兴奋性[60] [61]。在 PSE 治疗中，rTMS 可作用于癫痫病灶或相关脑区，抑制异常放电。有研究表明，rTMS 对部分 PSE 患者的癫痫发作频率和严重程度有一定的改善作用[62]，同时还可能对患者的认知功能和抑郁状态产生积极影响[63]。然而，rTMS 的治疗参数(如刺激频率、强度、时间等)尚未标准化，不同研究结果存在一定差异，需要进一步优化治疗方案[64]。

经颅直流电刺激(transcranial direct current stimulation, tDCS)通过在头皮表面放置电极，施加微弱的直流电，改变大脑皮质的兴奋性。在 PSE 治疗中，tDCS 可调节大脑皮质的神经可塑性[65]，抑制癫痫发作。虽然目前 tDCS 在 PSE 治疗中的应用研究相对较少，但已有一些初步证据显示其具有一定的治疗潜力。例如，有研究发现，对特定脑区进行 tDCS 刺激可减少癫痫样放电[66]。然而，tDCS 的长期疗效和安全性仍需更多研究证实[64]。

迷走神经刺激(vagus nerve stimulation, VNS)是一种通过植入式装置刺激迷走神经的治疗方法。在 PSE 治疗中，VNS 可调节脑内神经递质和神经肽的释放，抑制癫痫发作。一些临床研究表明，VNS 对部分难治性 PSE 患者有一定疗效，可减少发作频率，改善患者的生活质量[67] [68]。但 VNS 治疗也存在一些问题，如手术植入装置的风险、刺激参数的调整等，需要进一步规范和优化[69]。

这三种治疗方式均需进一步的临床研究。

4.3. 手术治疗

对于药物难治性 PSE 患者，手术治疗可作为一种选择。手术方式主要包括癫痫病灶切除术、前颞叶切除术、海马硬化切除术等[70]。癫痫病灶切除术适用于能够明确癫痫病灶且病灶位于非功能区的患者，通过切除病灶可有效控制癫痫发作。前颞叶切除术常用于治疗起源于颞叶的癫痫，可去除癫痫发作的起始部位和相关的致痫网络。海马硬化切除术则针对伴有海马硬化的 PSE 患者，切除病变的海马组织可减少癫痫发作[70] [71]。然而，手术治疗存在一定风险，如术后感染、出血、神经功能缺损等，需要严格掌握手术适应证，并在术前进行详细的评估和规划。

5. PSE 的预后因素

5.1. 卒中类型和严重程度

出血性卒中患者发生 PSE 的风险通常高于缺血性卒中患者[3]。这可能与出血性卒中导致的脑损伤更为严重，引发的炎症反应和神经递质失衡更显著有关[72]。在缺血性卒中中，大面积脑梗死、脑栓塞等严重类型的卒中患者发生 PSE 的概率也相对较高[73]-[75]。卒中严重程度通常采用美国国立卫生研究院卒中量表(NIHSS)评分进行评估，NIHSS 评分越高，表明卒中越严重，发生 PSE 的风险也越大[76]。此外，卒中部位也与 PSE 的发生密切相关[77] [78]，如皮质受累、颞叶、额叶等部位的卒中更容易引发癫痫发作。

5.2. 癫痫发作类型和频率

部分性发作的 PSE 患者预后相对较好，而全身性强直–阵挛发作或癫痫持续状态的患者预后较差[79]。频繁发作的患者往往需要更高剂量的抗癫痫药物治疗，且更容易出现药物不良反应，同时也增加了认知功能损害和心理障碍的风险[80]，进一步影响患者的预后。早发性癫痫发作和晚发性癫痫发作的预后也有所不同，早发性癫痫发作可能提示脑损伤更为严重，但部分患者在早期发作控制后，后期不再发作；而晚发性癫痫发作患者的癫痫可能更具慢性化趋势，治疗难度相对较大[8]。

5.3. 治疗时机和依从性

早期诊断和及时治疗对 PSE 患者的预后至关重要。在卒中后早期，积极控制癫痫发作可减少癫痫发作对脑功能的进一步损害，有利于神经功能的恢复。患者对抗癫痫药物的依从性也是影响预后的重要因素[81]。依从性差的患者容易出现漏服、自行停药等情况，导致癫痫发作控制不佳，增加复发风险，进而影响预后。因此，提高患者对疾病的认知和治疗依从性是改善 PSE 预后的关键环节之一。

6. 结论与展望

综上所述，卒中后癫痫的研究在病理生理机制、诊断方法、治疗策略和预后因素等方面取得了一定进展，但仍存在诸多挑战。在病理生理机制方面，虽然对神经递质失衡、离子通道异常、血脑屏障破坏和炎症反应等有了一定的认识，但这些机制之间的相互作用和具体的分子信号通路仍需进一步深入研究。诊断上，目前的脑电图、影像学和血液生物标志物检查各有其优势和局限性，需要开发更敏感、特异的诊断方法或联合诊断模式，以提高早期诊断的准确性。治疗方面，尽管有多种抗癫痫药物、神经调控技术和手术治疗方法可供选择，但仍缺乏针对 PSE 的特效治疗方案，且不同治疗方法的最佳适应证和治疗时机尚未明确。预后因素复杂多样，需要进一步建立综合、准确的预后预测模型，为临床决策提供更有力的支持。

未来的研究可集中在以下几个方面：一是深入探究 PSE 的发病机制，尤其是在分子生物学和遗传学层面，寻找新的治疗靶点；二是开展大规模、多中心的临床试验，比较不同治疗方法的疗效和安全性，优化治疗方案；三是加强对 PSE 患者的长期随访研究，进一步明确预后因素，建立有效的预后预测模型；四是探索新的诊断技术和生物标志物，提高 PSE 的早期诊断率。通过这些研究方向的努力，有望提高卒中后癫痫的诊疗水平，改善患者的预后和生活质量。

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