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成人癫痫合并认知功能障碍危险因素进展

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摘　要

癫痫患者中60%~70%存在认知障碍，严重影响生活质量。本文系统综述了癫痫患者认知功能障碍相关危险因素。发现癫痫相关因素包括：局灶性癫痫(尤其额、颞叶)认知损害更显著，表现为语言、执行功能缺损；全身性癫痫通常与丘脑－皮质网络异常相关。高频发作及长病程显著加剧认知衰退，可能与异常放电累积损伤相关。抗癫痫药物(AEDs)：传统AEDs (如丙戊酸、卡马西平)及多药联用对认知损害较大；新型AEDs (如左乙拉西坦、吡仑帕奈)影响较小或中性，但托吡酯可能损害执行功能。年龄增长和低教育水平是独立危险因素，后者与脑白质损伤代偿能力下降相关。抑郁、焦虑状态与认知评分显著负相关；睡眠障碍(如纺锤体活动降低)直接损害注意力与记忆。最新研究表明缺乏锻炼加重认知损伤，规律运动可改善执行功能；肠道菌群失调及血管风险(肥胖、高血压、吸烟)通过神经炎症或血流障碍加剧认知衰退。认知障碍是多重因素交互作用的结果，未来需建立预测模型实现早期干预，并积极推广健康生活方式。

关键词

癫痫，认知功能障碍，危险因素，机制

Progression of Risk Factors for Adult Epilepsy with Cognitive Dysfunction

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Abstract

60%~70% of patients with epilepsy have cognitive impairment, which seriously affects their quality

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of life. This article systematically reviews the risk factors associated with cognitive dysfunction in patients with epilepsy. Epilepsy-related factors were found to include: focal epilepsy (especially frontal and temporal lobes) has more significant cognitive impairment, manifested as language and executive function deficits; Generalized epilepsy is often associated with abnormalities in the thalamic-cortical network. Frequent episodes and long course of the disease significantly exacerbate cognitive decline and may be associated with cumulative damage from abnormal discharges. Antiepileptic drugs (AEDs): Traditional AEDs (such as valproic acid, carbamazepine) and polypharmacy have significant cognitive impairment; Newer AEDs (e.g., levetiracetam, perampanel) have a low or neutral impact, but topiramate may impair executive function. Increasing age and low education levels are independent risk factors, the latter associated with reduced compensatory capacity for white matter damage. Depression/anxiety state was significantly negatively correlated with cognitive scores. Sleep disturbances (e.g., decreased spindle activity) directly impair concentration and memory. The latest research shows that lack of exercise aggravates cognitive impairment, and regular exercise can improve executive function; Dysbiosis of the gut microbiota (e.g., Collinsella abnormalities) and vascular risk (obesity, hypertension, smoking) exacerbate cognitive decline through neuroinflammation or impaired blood flow. Cognitive impairment is the result of the interaction of multiple factors, and in the future, predictive models need to be established to achieve early intervention, control comorbidities, and actively promote healthy lifestyles.

Keywords

Epilepsy, Cognitive Dysfunction, Risk Factors, Mechanisms

1. 引言

癫痫是一种常见的脑部疾病，常常表现为自发性反复发作的短暂体征或精神症状[1]。据统计，中国约有 1000 万癫痫患者。出生时的损伤或之后的损伤、血管原因和中枢神经系统感染是最常见的危险因素[2]。持续的癫痫发作会对大脑造成不可逆的损害，导致认知功能障碍和整体智力缺陷[3]。60%~70%的癫痫患者存在认知障碍，主要表现为记忆力、注意力、语言等功能障碍，严重影响生活质量，导致残疾甚至死亡[4]。目前普遍认为认知障碍是多种因素共同作用的结果，本文旨在对成人癫痫患者认知功能障碍相关危险因素进展进行综述。

2. 癫痫相关危险因素

2.1. 癫痫类型

根据国际抗癫痫联盟 2017 年分类标准，癫痫可分为局灶性、全身性和不明发作性三类[5]。有一项横断面研究通过对 495,149 名参与者 10 年多的随访证实无论心血管风险水平高低，患有局灶性癫痫患者相比无局灶性癫痫患者认知障碍的程度更高[6]。Kayela 等对 106 名额叶癫痫患者完成了包括认知功能的神经心理学测试，识别出四个特殊认知表型，同时发现语言是额叶癫痫中最突出的认知领域特异性损伤，其次是注意力、执行功能[7]。颞叶癫痫作为最常见的局灶性发作类型，主要表现为执行功能障碍，且高磷酸化的 tau 蛋白存在会增加认知能力下降的风险[8]。丘脑皮质被认为是维持全身性癫痫发作的关键，对全身性癫痫患者进行中央正中（CM）丘脑刺激后癫痫患者的认知症状得到改善，该影响被认为是由 CM 广泛的皮质连接介导的，包括前额叶、眶额叶、岛叶、运动和感觉皮层[9]。

2.2. 癫痫发作频率

有证据表明癫痫发作频率也是癫痫患者认知障碍的危险因素之一。Foster 等研究招募 331 例癫痫患者并评估客观认知功能、主观认知功能的生活质量量表以及焦虑和抑郁症状问卷，发现癫痫发作频率是导致客观和主观认知功能障碍的重要决定因素[10]。Gavrilovic 等通过记录 12 个月和 18 个月药物敏感和耐药癫痫患者 MOCA 评分随访结局证明癫痫发作频率越高，认知障碍更严重[11]。Ifrah Zawar 等人分析了入组时认知正常的 13,726 名癫痫患者，最终结局是认知障碍，发现在过去的一年内有癫痫发作的患者比没有癫痫发作患者早期认知功能下降风险更高[12]。原因可能是频繁的癫痫发作延长了脑灰质异常放电的时间，从而导致认知功能下降[13]。

2.3. 抗癫痫药物

抗癫痫药物的使用作为癫痫患者最主要的治疗方法，也被证实与认知功能障碍相关。目前普遍认为第一代抗癫痫药物包括丙戊酸、卡马西平等对认知功能的影响更大。KJ 等发现 316 名暴露于丙戊酸盐的儿童与暴露于卡马西平、拉莫三嗪和苯妥英的儿童相比，丙戊酸与认知领域功能的降低呈现出剂量相关性，而且丙戊酸组的语言功能明显低于其他三组[14]。Simeone 和 Timothy 等发现高浓度的卡马西平会对癫痫患者认知功能产生损害[15]。第二代抗癫痫药物包括奥卡西平、左乙拉西坦、托吡酯等。奥卡西平未发现对认知功能的影响[16]。一项有关左乙拉西坦的荟萃分析认为左乙拉西坦可能改善癫痫患者的执行功能[17]。而一项回顾性分析结果认为左乙拉西坦对认知功能的影响呈负性，该研究把 221 名癫痫患者分为四组：无药物组、非左乙拉西坦药物组、高剂量组和低剂量左乙拉西坦组，综合评分发现高剂量左乙拉西坦组认知领域得分更低[18]。有证据表明托吡酯对执行功能有负面影响[19]。第三代药物吡仑帕奈被认为对癫痫患者认知功能的影响是中性效应，没有恶化或者改善[20]。除 AED 的不同种类，AED 的数量也被证实对认知功能有影响。Wang Lei 等对 257 名癫痫患者的认知障碍因素评估发现 AED 多药治疗影响癫痫患者的记忆、注意力和执行功能等神经认知功能，而且不良反应事件明显多于单药治疗[13]。一项大型横断面研究纳入了波恩大学医院 834 名癫痫患者认知评估数据，发现认知功能结果与 AED 数量呈负性相关，而且每增加一种药物，执行功能下降更加显著[21]。这可能与多种药物联合使用时药物的认知风险的累积有关[13]。因此在使用抗癫痫药物治疗过程中，应尽可能选择对认知障碍损害轻的药物，并且控制药物种类的数量。

2.4. 癫痫发作病程

癫痫发作病程越长，癫痫患者认知功能受损程度更高。Huang Hui 等对 80 例癫痫患者和 70 例健康受试者的蒙特利尔认知评估、汉密尔顿焦虑、抑郁评分量表对照评估发现认知功能障碍与病程持续时间呈负相关[22]。Roy C 等对老年癫痫患者 27 人和健康老年人 27 人检查癫痫发作持续时间与认知测试表现之间关系的相关分析中，发现癫痫发作持续时间越长，认知功能障碍程度越重。但该研究缺点在于收集样本数量较少，在准确性上可能略差[23]。

3. 基础因素

有研究发现相比年轻人，老年人更容易发生癫痫发作、认知功能障碍，而且认知功能障碍程度随年龄增长呈正相关[24]。认知功能损害区域主要是在视觉记忆、注意力和执行功能方面[25]。较低的教育水平已被证实与癫痫患者认知功能障碍相关。对 257 例癫痫患者用不同临床记忆量表测评认知功能，结果发现较低的教育水平与认知障碍严重程度呈正相关，而高中及以上的文化程度对癫痫患者的认知功能是保护因素[13]。原因可能是一教育程度高的人可以理解和配合测试，测试的结果更加可靠[8]；二是较高的

教育水平会减少脑室周围白质高信号对认知功能的负面影响[26]。因此，社会应该增加对于教育程度受限的老年癫痫患者关注，努力提高癫痫患者的平均受教育水平，控制认知障碍的进展。

4. 共病因素

4.1. 抑郁、焦虑状态

抑郁和焦虑是癫痫患者最常见的精神并发症，而焦虑和抑郁状态对癫痫患者的认知功能表现有负面作用[13]。Nolan 等对 826 名癫痫患做了神经心理学评估发现不论是基于 BDI-2 原始评分、BDI-2 临界评分或 BDI-2 严重程度类别中任意一种得到的抑郁评分，抑郁症状越多的癫痫患者认知表型得分越低[27]。导致抑郁的可能与失业或社交能力下降等因素有关。Miller 等分析了 38 名老年癫痫患者和 29 名健康对照者，发现更高水平的焦虑与较差的视觉记忆分数有关，证明了焦虑也是老年人癫痫患者认知缺陷的危险因素[25]。但是现实生活中大多数患者的心理问题经常被忽视，直到严重影响生活质量，而往往这个时候的干预可能不会起到应有的效果。因此，早期发现并干预治疗心理疾病对减轻癫痫患者认知功能的损害十分有必要。

4.2. 睡眠障碍

越来越多的研究表明睡眠障碍会增加癫痫患者认知障碍的风险。癫痫患者大多数存在行为异常，会导致较差的睡眠质量，而不良的睡眠模式会导致注意力不集中、记忆力问题等。长期慢性睡眠剥夺会对癫痫患者的生活质量和认知功能产生不良影响[28]。Huang Yajin 等记录了 57 名成年癫痫患者在完成认知测试后 6 小时内的整夜睡眠脑电图数据，比较不同认知障碍严重程度 N2 睡眠期间头皮水平睡眠纺锤体活动的空间分布特征，发现随着认知障碍严重程度的进展，快慢纺锤体密度逐渐降低，而纺锤体率越低神经认知功能损害越重[29]。

5. 生活方式

5.1. 缺乏体育锻炼

目前研究发现癫痫患者在空闲时间体育活动频率越低，癫痫持续时间越长，对认知功能损害越大[30]。2016 年国际抗癫痫联盟发布指南支持癫痫患者定期锻炼的观点，认为有利于提高癫痫患者自尊、社交，并改善长期整体健康，另外还为不同运动程度提供了建议[31]。Feter 等把身体不活跃的受试者随机分为两组，一组在实验期间保持日常活动。一组进行 12 周的体育训练，分别记录基线数据和 12 周后的数据，发现定期体育锻炼会改善成人癫痫患者的执行功能[32]。Doseva 等对毛果芸香碱诱导的癫痫持续发作小鼠在发作前 4 周和后 8 周进行长期有氧训练，发现癫痫发作前后的耐力训练对多个认知领域有显著的改善[33]。但是与普通人群相比，癫痫患者的身体活动依然偏少。因此对癫痫患者更应该鼓励他们进行体育锻炼。

5.2. 肠道菌群失衡

Johnson 等认为微生物会通过微生物群－肠道－大脑轴调节大脑功能和行为[34]。肠道菌群可促进神经系统的成熟、保护肠道神经元，但是肠道微生物合成的某些代谢物一旦过量反而会对神经元造成损失[35] [36]。洪秉聪等人做的一项横断面研究把研究对象分为癫痫组和健康对照组各 100 例，再将癫痫组分为合并认知障碍组和无认知障碍组，发现癫痫组存在菌群失调，而 Collinsella、Oscillospirales 和 Ruminococcaceae 这三种菌群对癫痫合并认知障碍患者影响很大[37]。Muhammad Usma 等把小鼠分为不同药物组发现长期口服益生菌作为抗癫痫药物辅助治疗会减轻戊四唑诱导的神经精神障碍，包括焦虑、

抑郁以及认知缺陷[38]。因此在未来有希望把肠道微生物作为干预目标来降低认知功能障碍的程度。

5.3. 血管危险因素

最近有研究发现肥胖、高血压、中风史、血脂异常、吸烟史等血管危险因素也被认为对患有癫痫的老年人的认知功能有影响。Tedrus 等对 164 例癫痫患者分析发现超过一半的人都是超重/肥胖，而这些人群的认知功能障碍程度也更重[39]。Choi 等收集了 5888 名 ≥ 65 岁的美国成年人，通过建立模型分析癫痫和血管危险因素与认知能力下降的个体和联合关联，发现同时患有癫痫和高血压的组比仅患有两者之一或两者都没有的组随着时间的推移认知能力下降的速度更大，而且既往有中风史的癫痫患者的信息处理速度下降幅度也大于预期值[40]。合并认知功能障碍的癫痫患者的血清载脂蛋白 E 水平显著高于健康受试者，而且血清载脂蛋白水平与认知程度呈显著负相关[41]。在当前吸烟者中，癫痫与整体认知能力下降有很强的相关性[42]，这可能因为尼古丁和烟草烟雾具有促惊厥作用[43]。

6. 总结

综上所述，目前公认的癫痫合并认知功能障碍的危险因素包括癫痫发作类型、癫痫发作频率、抗癫痫药物的使用、癫痫发作持续时间。然而，基于现有研究的研究人群、方法学及样本规模上存在显著差异，关键因素的作用机制与交互效应仍需进一步验证。因此，未来研究应优先聚焦以下方向：1、积极开展大型多中心前瞻性队列研究，探究低教育水平与特定 AEDs (如托吡酯、苯巴比妥)认知毒性的协同作用，抗癫痫药物与焦虑、抑郁、睡眠障碍等共病之间的交互作用；2、整合额颞叶癫痫定位、发作频率、共病抑郁状态等核心变量，结合脑电图等动态指标，使用机器学习等开发构建成人癫痫合并认知功能障碍的危险预测模型；最终达到对成人癫痫合并认知功能障碍早期防治的目的。

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