

癫痫共患抑郁情绪的研究进展

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摘 要

癫痫患者在神经科是很常见的, 癫痫患者一经确诊, 就会面临巨大的心理压力。患者常常失去了开车的权力, 也不能饮浓茶、咖啡、可乐等, 甚至不能单独洗澡。癫痫患者常常伴有抑郁情绪, 抑郁情绪比抑郁症病情稍轻, 主要表现为稍长时间的情绪低落、兴趣丧失、睡眠障碍、自杀意向。若未及时发现, 长此以往, 则会使患者病情恶化, 甚至引起患者自杀。本文从癫痫共患抑郁的流行病学、发病机制、危险因素、筛查、治疗等方面综述, 为临床医生提供帮助。

关键词

癫痫, 癫痫共患病, 抑郁, 发病机制, 诊断, 治疗

Research Progress of Depressive Emotion in Patients with Epilepsy

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Abstract

Patients with epilepsy are quite common in the neurology department. Once diagnosed, they will face tremendous psychological pressure. They are often unable to drive, not allowed to drink strong tea, coffee, cola, etc., and may even be unable to take a bath alone. Patients with epilepsy are often accompanied by depressive emotions, which are a bit milder than depression, mainly shown as relatively long-term low mood, loss of interest, sleep disorders, and suicidal intentions. If not detected in time, as time passes, the patient's condition will worsen and may even lead to the patient's suicide. This article reviews the epidemiology, pathogenesis, risk factors, screening, and treatment of

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epilepsy comorbid with depression, so as to assist clinicians.

Keywords

Epilepsy, Epilepsy Comorbidity, Depression, Pathogenesis, Diagnosis, Treatment

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1. 引言

伴有抑郁情绪的癫痫患者(Patients with Epilepsy, PWE)很多。抑郁情绪不仅使 PWE 的自杀风险增加,还可使疾病进一步恶化。目前,癫痫共患抑郁情绪在我国的研究仍不充分,临床医生未能充分识别此类患者,使得临床上漏诊率高,患者病情未能得到及时的医治。

2. 癫痫共患抑郁的流行病学

在 PWE 中,共患抑郁的患者很常见。波兰格但斯克市 96 例 PWE 中 8.3%的患者同时患有重度抑郁障碍和焦虑障碍,50.0%的焦虑障碍患者同时患有重度抑郁障碍[1]。在丹麦全国范围内的 139,014 例 PWE 的研究中,PWE 共患抑郁的风险是匹配对照组的 1.88 倍(95%CI 1.82~1.95) [2]。韩国首尔 134 例 PWE 中抑郁患者占 14.0% [3]。印度孟买地区 96 例 PWE 中 36.5%的患者合并抑郁,29.2%的 PWE 合并焦虑[4]。沙特阿拉伯塔伊夫市 150 例 PWE 发现 76.7%的患者患有抑郁,8.7%患有严重抑郁,13.3%患有中重度抑郁[5]。非洲卢旺达基加利 572 例 PWE 中抑郁症和中重度抑郁的流行率分别为 14.2%和 4.7% [6]。我国甘肃省研究发现 335 例 PWE 中抑郁共患率为 58.8%,其中轻度、中度和重度共患率分别为 29.9%、17.0%和 11.9% [7]。此外,我们也应该注意女性和儿童癫痫共患抑郁的情况。研究发现成年女性 PWE 患抑郁症的风险是成年男性 PWE 的 4.27 倍[8];癫痫儿童中有 20.0%均达到重度抑郁症的临床阈值[9]。

3. 癫痫共病抑郁患者的生活质量

生活质量可以衡量个体的生活状态和幸福程度,它是个体在生理、心理、社会等多个方面的综合体验。抑郁会降低 PWE 的生活质量[10]-[12],其中,抑郁情绪的严重程度、躯体症状的数量和严重程度及近一年癫痫发作频率是影响 PWE 生活质量的重要因素[13] [14]。研究发现,PWE 的生活质量与抑郁症状的关联比癫痫发作频率更强[15]。而且,抑郁会引起 PWE 自杀[16]。有研究表明,社会支持感知力损害是 PWE 自杀风险较高的预测因素之一[17] [18],患者的社会支持感知力下降可能导致社会孤立,进而使患者抑郁,最终导致患者自杀[17] [18]。

4. 癫痫共患抑郁的发病机制

癫痫共患抑郁的机制仍在研究中,目前可能的发病机制主要有以下几种。

4.1. 神经炎症

小胶质细胞介导的神经炎症反应与 PWE 的抑郁情绪紧密相关。与这些神经炎症反应相关的小胶质细胞分为两种,即 M1 经典型和 M2 替代型。M1 型活化后释放炎症介质(白细胞介素-6、白细胞介素-1 β 等),引起炎症和神经损伤;M2 型活化后释放抗炎介质(如脑源性神经营养因子等),起到抗炎和神经保护

作用[19]。M1 型和 M2 型小胶质细胞间促炎与抗炎的平衡与 PWE 共患抑郁密切相关。相关研究发现,与无抑郁样行为的小鼠相比,经戊四氮诱导出抑郁样行为的小鼠癫痫发作程度更加严重,海马区促炎因子的表达更多,M1 型小胶质细胞介导神经炎症反应更加活跃[20]。另一研究发现,癫痫共病抑郁组大鼠体内促炎因子诱导型一氧化氮合酶表达明显增多,抗炎因子精氨酸酶 1 表达明显减少,且共病组大鼠 M1 型小胶质细胞表达升高,共病组 M1 和 M2 的炎症与抗炎的平衡被打破[21]。

但癫痫严重程度和精神疾病共病的生物标志物仍未确定。McGonigal 等为了研究脑源性神经营养因子是否可以作为癫痫严重程度和精神疾病共病的生物标志物,结果发现服用了抗癫痫药物的患者血清脑源性神经营养因子水平升高,但未证实脑源性神经营养因子与癫痫严重程度或精神共病的关联,未来研究需控制抗癫痫药物的使用以进一步探讨脑源性神经营养因子作为癫痫严重程度和精神共病潜在生物标志物的作用[22]。

4.2. 下丘脑 - 腺垂体 - 靶轴活跃

PWE 出现抑郁情绪时,下丘脑 - 腺垂体 - 肾上腺轴常常高度活跃,引起皮质醇水平升高。相关研究发现,局灶性癫痫、癫痫和共病抑郁症和重度抑郁症患者的血皮质醇水平升高,且重度抑郁的患者血皮质醇与促肾上腺皮质激素呈正相关,证实了下丘脑 - 腺垂体 - 肾上腺轴在癫痫和抑郁症发病机制中的作用[23]。糖皮质激素受体蛋白的表达是由下丘脑 - 腺垂体 - 肾上腺轴激活引起的,糖皮质激素受体功能障碍可以导致下丘脑 - 腺垂体 - 肾上腺轴负反馈受损,进而导致下丘脑 - 腺垂体 - 肾上腺轴前馈激活。研究发现,PWE 海马区糖皮质激素受体的表达下降,癫痫伴抑郁的患者海马区糖皮质激素受体免疫反应性低于癫痫不伴抑郁患者,这说明了下丘脑 - 腺垂体 - 肾上腺轴在癫痫共患抑郁的发病过程中的确发挥着不可或缺的作用[24]。

在女性 PWE 中,下丘脑 - 腺垂体 - 性腺轴与抑郁相关。研究发现,催乳素和睾酮水平的变化是女性 PWE 抑郁症的重要生物标志物[25]。催乳素是预测女性癫痫患者抑郁症的因素之一。催乳素与多巴胺水平呈负相关,抑郁患者中催乳素水平升高可能导致多巴胺水平降低,进而引起更高的抑郁症状。催乳素的变化可能影响下丘脑 - 垂体 - 卵巢轴的功能,导致雌激素、孕激素等激素水平的改变,从而影响患者的情绪状态。例如,催乳素升高可能抑制黄体生成素和卵泡刺激素的释放,进而影响睾酮的产生,间接影响患者的抑郁状态。睾酮也是预测女性癫痫患者抑郁症的因素之一。睾酮具有神经保护作用,能够通过增加新生神经元的存活来促进神经生长,可以改善因癫痫和抑郁导致的神经功能损伤。睾酮水平的变化可能通过影响下丘脑 - 垂体 - 性腺轴,间接影响其他激素的分泌,从而对情绪产生影响。

4.3. 神经传递障碍

4.3.1. 5-羟色胺系统和内源性大麻素系统

5-羟色胺(5-Hydroxytryptamine, 5-HT)和内源性大麻素系统密切相关,共同在癫痫共患抑郁中发挥着作用。内源性大麻素系统由受体、配体和相关酶组成,其中大麻素受体 1 和 2 分别位于神经元末梢和免疫细胞。内源性大麻素系统通过多种方式影响 5-HT 传递、释放、受体表达和功能,5-HT 也会触发大麻素受体的内源性配体 2-花生四烯酸甘油的释放,进而影响大麻素受体 1 受体活性及内源性大麻素系统的表达和功能。内源性大麻素系统的改变与抑郁行为有关,增强内源性大麻素信号或 5-HT 神经传递可以产生抗抑郁效果[26] [27]。5-HT 和内源性大麻素系统在癫痫的病理生理机制中都起着重要作用,并且两者之间存在相互作用,这将成为癫痫治疗的新靶点[26]。

4.3.2. 多巴胺能系统

Rocha 等研究颞叶癫痫共患抑郁患者的颞皮层,发现内侧颞叶癫痫患者的新皮层中多巴胺 D1 受体表

达和结合升高,多巴胺 D2 受体则降低,继发于脑瘤或病变的颞叶癫痫患者的新皮层中多巴胺 D1 受体高表达和多巴胺 D2 受体样诱导的 G 蛋白激活。两组患者的多巴胺转运蛋白结合增加,多巴胺及其代谢物的组织含量较低,这表明由多巴胺能系统紊乱引起的癫痫发作可能在共病机制中发挥作用[28]。

4.3.3. 谷氨酸能系统

癫痫共患抑郁时,患者体内谷氨酸代谢增高。有研究表明谷氨酰胺异常及其代谢水平与抑郁严重程度呈正相关[29]。还有研究显示,抑制杏仁核内谷氨酰胺合成酶可导致癫痫大鼠在癫痫发作时出现快感缺乏的情况[30]。N-甲基-D-天冬氨酸受体 1 是谷氨酸受体的一个亚基,研究发现,抗抑郁药可以使癫痫共患抑郁的患者海马齿状回分子层的 N-甲基-D-天冬氨酸受体 1 显著下降[31]。此外,癫痫共患抑郁时,患者体内血脑屏障会被破坏。血脑屏障的破坏包括急性和慢性阶段。急性阶段表现为通透性短暂增加,慢性阶段则是由于反复的癫痫发作导致细胞因子释放、自由基产生和周细胞功能改变,进而破坏细胞外基质和血脑屏障完整性。这会导致谷氨酸清除能力下降,进一步促进神经精神症状的发展[32]。

4.3.4. 其他系统

癫痫共患抑郁的患者可能有较低水平的 γ -氨基丁酸和 γ -氨基丁酸受体变化。Rocha 等研究了 26 例耐药 PWE 的颞叶皮层标本,发现抑郁患者的组织中 γ -氨基丁酸含量减少,编码 $\gamma 2$ 亚基的 mRNA 表达增加, γ -氨基丁酸 B 型受体诱导的 G 蛋白减少[33]。此外,在遗传性癫痫易感大鼠模型中,去甲肾上腺素的传递普遍减少,提示去甲肾上腺素可能参与共病[34]。

4.4. 特定基因

癫痫共患抑郁与特定基因有关。Rayiky 等在使用有限的被褥和筑巢条件模型的早期生活逆境研究中,发现早期生活逆境改变了与应激反应相关基因的表达,加速了癫痫的发生,增加了疾病的严重程度,影响 HPA 轴功能,并导致癫痫大鼠出现抑郁样行为[35]。Yu 等人通过对基因表达数据集的分析,发现 Arc 和 Homer1 基因可能与癫痫共患抑郁有关[36]。

5. 癫痫共患抑郁的影响因素

有很多因素对癫痫共患抑郁有影响。研究表明,女性 PWE 相较于男性 PWE 更容易患抑郁[37][38]。其中,低社会经济地位、癫痫持续时间、发作频率、发作类型、抗癫痫药物使用数量等是癫痫共患抑郁的风险因素[36][38]。女性、有热性惊厥病史、抗癫痫药物有副作用以及存在从局灶性有意识发作到局灶性意识受损发作再到双侧强直-阵挛发作的组合是癫痫患者抑郁症状的独立预测因素[37]。抑郁与睡眠质量差相关,且二者都与癫痫控制不佳有关;非依从性与抑郁和睡眠质量差相关,也是癫痫控制不佳的预测因素之一[36]。

6. 癫痫共患抑郁的筛查诊断方法

PWE 共患抑郁症应由精神科医生诊断,对于未达到诊断标准的患者称为抑郁状态或抑郁情绪。诊断标准为国际疾病分类(International Classification of Diseases, ICD)-10 和精神疾病诊断与统计手册(Diagnostic and Statistical Manual of Mental Disorders, DSM)-V [39]。此外,如医院焦虑抑郁量表(Hospital Anxiety and Depression Scale, HADS)、汉密尔顿抑郁量表(Hamilton Depression Rating Scale, HAMD)、简明国际神经精神访谈(Mini International Neuropsychiatric Interview, MINI)、贝克抑郁量表(Beck Depression Inventory, BDI)-II、患者健康问卷(Patient Health Questionnaire, PHQ)-9 和癫痫神经障碍抑郁量表(Neurological Disorders Depression Inventory for Epilepsy, NDDI-E)等作为筛查工具也常常应用于临床和科研工作中[40]-[44]。国际抗癫痫联盟(International League Against Epilepsy, ILAE)推荐使用 NDDI-E 作为筛查 PWE 患者严重抑

郁发作的工具[45]。对于儿童癫痫共患抑郁, Wagner 等人对美国常用的 9 种儿童癫痫行为健康筛查工具进行评估, 发现青少年癫痫神经障碍抑郁量表(Neurological Disorders Depression Inventory for Epilepsy-Youth, NDDI-E-Y)和儿童神经生活质量抑郁量表(Pediatric NeuroQoL-Depression)是在癫痫儿童中验证良好的抑郁筛查工具[46]。

7. 癫痫共患抑郁的治疗

7.1. 药物治疗

很多抗癫痫药物, 如巴比妥类、环己烯酸、唑尼沙胺、托吡酯、左乙拉西坦等, 都会对 PWE 的情绪造成负面影响, 应避免使用。但也有一些抗癫痫药物, 如丙戊酸钠、拉莫三嗪可以改善 PWE 的抑郁情绪[39]。ILAE 建议, 癫痫共患抑郁患者的一线治疗方法为选择性 5-羟色胺再摄取抑制剂(Selective Serotonin Reuptake Inhibitors, SSRIs) [47]。在 SSRIs 中, 舍曲林和西酞普兰因其与抗癫痫药物的相互作用较少等优点, 推荐使用[39]。

然而, 现有的抗抑郁药物治疗癫痫有效性的证据非常有限。Maguire 等[48]系统回顾了抗抑郁药物治疗 PWE 抑郁症的随机对照试验和前瞻性队列研究, 他们发现, 只有一项随机对照试验证明了文拉法辛对抑郁症的统计显著作用, 仍然缺乏高质量的研究来提供关于抗抑郁药物的安全性、选择和类别的进一步信息。

7.2. 认知行为疗法

认知行为疗法(Cognitive Behavioral Therapy, CBT)能够通过改变患者不合理的认知来减轻 PWE 的抑郁程度。CBT 结合家庭治疗常常用于治疗儿童和青少年癫痫共患抑郁[49]。Choudhary 等人对 13 项随机对照试验进行 meta 分析, 研究 CBT 对 PWE 抑郁和焦虑的影响。结果显示, CBT 对 PWE 的焦虑和抑郁治疗有效, 并能提高生活质量, 但研究存在样本量差异等局限性, 未来需要更多高质量研究[50]。

CBT 中互联网干预(Emyna)是一种基于 CBT 技术的全自动数字干预措施, Meyer 等人进行了一项随机对照试验, 检验了癫痫特定 Emyna 在减轻抑郁症状、焦虑症状以及提高生活质量方面的功效。结果显示, 干预组在抑郁、焦虑、压力、社会职业障碍和癫痫相关生活质量方面均有显著改善, 效果量超过临床相关阈值, 且在 3 个月时干预组参与者报告的因病休假天数和住院天数更少。这些结果表明 Emyna 对改善 PWE 的心理健康和生活质量有效[51]。

7.3. 迷走神经刺激法

从 19 世纪末用于治疗癫痫的叉状装置到 1985 年现代侵入性迷走神经刺激设备, 迷走神经刺激法经历了快速的发展。今天, 我们所运用的迷走神经刺激法又分为侵入性迷走神经刺激(Invasive Vagus Nerve Stimulation, i-VNS)和非侵入性迷走神经刺激。它们在癫痫、抑郁等的治疗中均发挥着重要作用[52]。i-VNS 是一种有创的方法, 它通过手术将在左胸上部或左腋窝边界植入脉冲发生器, 刺激左颈中部迷走神经来发挥作用。诱导或加重睡眠呼吸暂停是它常见的并发症, 但最新研究发现, i-VNS 会伴发呃逆这一罕见但可能的副作用[53]。非侵入性迷走神经刺激分为经皮颈部迷走神经刺激和经皮耳迷走神经刺激(Transcutaneous Auricular Vagus Nerve Stimulation, ta-VNS)。有研究表明 ta-VNS 对癫痫和抑郁患者的治疗均有效[54]。ta-VNS 是无创的, 它与 i-VNS 不同, 是通过附着在左耳耳甲腔皮肤的双极电极刺激迷走神经的耳支来发挥作用的, 无需像 i-VNS 那样进行植入手术, 从而避免了手术相关的风险以及术后因手术和技术原因导致的并发症。Yang 等人进行了一项随机双盲临床试验, 研究 ta-VNS 对耐药性癫痫的治疗效果。结果表明, ta-VNS 治疗耐药性癫痫效果明显[55]。

8. 总结与展望

癫痫与抑郁存在某些共同的发病机制，癫痫患者极易产生抑郁情绪。为避免癫痫患者病情恶化乃至出现死亡的情况，每一位癫痫专科医生都需重视癫痫患者的心理健康状况。弄清癫痫与抑郁的微观联系，对其诊断，运用药物、认知行为疗法、迷走神经刺激等方法进行干预，从而提高患者的生活质量。未来，相信我们一定能够解开癫痫共患抑郁之谜。

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