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伴中央－颞区棘波的自限性癫痫发病机制、共患病及药物治疗进展

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摘　要

伴中央－颞区棘波的自限性癫痫是儿童最常见的癫痫综合征，以自限性癫痫发作为主要特征，可伴有不同程度的精神、行为及认知障碍。其发病机制可能与遗传因素、大脑微结构损伤、大脑功能网络受损等相关，同时其可合并行为认知等方面并发症，对于患者生活质量有不同程度的影响，抗发作药物治疗的时机、方案还缺乏可靠证据支持。本文通过对伴中央颞区棘波的自限性癫痫最新文献查阅，拟对其发病机制、共患病及治疗方案做一综述。

关键词

伴中央－颞区棘波的自限性癫痫，发病机制，共患病，药物治疗

Progress in Pathogenesis, Comorbidity and Drug Treatment of Self-Limited Epilepsy with Centrotemporal Spikes

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Abstract

Self-limiting epilepsy with centrotemporal spikes is the most common epilepsy syndrome in children, with self-limited seizures as the main feature, and can be accompanied by different levels of mental, behavioral and cognitive disorders. Its pathogenesis may be related to genetic fac-

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tors, brain micro-structure damage, brain functional network damage, etc. At the same time, it can be combined with behavioral cognitive and other complications, which have different degrees of impact on the quality of life for patients. The timing and plan of anti-epileptic drug treatment still lack reliable evidence support. This article reviews the pathogenesis, comorbidity and treatment of self-limited epilepsy with central temporal spikes by reviewing the latest literature.

Keywords

Self-Limited Epilepsy with Centrotemporal Spikes, Pathogenesis, Comorbidity, Medication

1. 引言

伴有中央－颞区棘波的自限性癫痫(Self-limited epilepsy with centrotemporal spikes, SeLECTS)，过去称为伴中央颞区棘波的良性癫痫(Benign epilepsy with centrotemporal spikes, BECT) [1]，近些年的研究在癫痫发作频率、病情进展，伴有的神经心理障碍方面均报道了更为严重的后果，故 2022 年国际抗癫痫协会在新的分类中使用“自限性”一词取代“良性”。同时 SeLECTS 在语言障碍、脑电图睡眠期持续癫痫样放电等表现与获得性癫痫失语综合征(Landau-Kleffner syndrome, LKS)、癫痫伴慢波睡眠期持续棘慢波(epilepsy with continuous spikes and waves during slow sleep, CSWS)等综合征有部分重叠，临床研究中约 6.6%的 SeLECTS 患者符合更严重的癫痫性脑病的标准[2]，有学者提出应将其视为癫痫－失语症谱系疾病中表现较轻的癫痫性脑病。

SeLECTS 的发病机制尚不完全明确，可能涉及复杂的遗传机制，近期研究提出大脑微结构异常及功能网络的等存在异常，可能与 SeLECTS 患者癫痫发作及其合并的一系列认知障碍相关。发病机制的探讨对于提供治疗思路及改善预后至关重要。同时 SeLECTS 合并的神经心理损害如注意力缺陷、语言障碍等已被广泛报道，其对于学龄前及学龄期儿童的技能学习、社交发展等均有影响，对于这些共患病的系统认知有助于临床中及时识别及积极干预，对于提升患者生活质量具有重要意义。另外临床中超过 2/3 的 SeLECTS 患者接受了抗发作药物治疗[3]，但对于典型 SeLECTS 是否应启用药物治疗仍存争议[4]，药物治疗时机及方案尚无可靠证据。本文就目前报道的发病机制、共患病及药物治疗情况进行综述。

2. SeLECTS 的发病机制

SeLECTS 可能存在复杂的遗传背景，但目前报道的可能相关的基因突变如 GRIN2A、ELP4、CHRNA5、PRRT2、SRPX2 等均在 LKS、CSWS 等更为严重的癫痫－失语症谱系疾病表型中更常见[5]，Lemke 等人报道了 GRIN2A 在 CSWS 患者中突变率约有 17.6%，而典型的 SeLECTS 患者中仅约 4.9% [6]，另一项研究中 11.1%的 LKS 和 7.1%的 ABPE 中检测到 GRIN2A 突变，而典型 SeLECTS 患者中未发现[7]，同样的有研究分析 PRRT2、ELP4、SRPX2 等单基因突变与癫痫 SeLECTS 的关联后发现这些基因与 SeLECTS 并无关联，Shi 等人也在一项大规模全基因组关联研究中经比对后未发现主要致病基因，提出 SeLECTS 的遗传可能为多种常见基因突变共同导致，同时报道了母亲在出生时吸烟可使 BECTS 风险增加 3.9 倍[5]；表明对于典型 SeLECTS 可能有必要进行进一步的多基因共同作用及表观遗传的分析，而目前报道的单基因突变可能仅对后续非典型进展及认知障碍具有提示作用。

SeLECTS 患者大脑白质存在微观结构的改变，尤其是丘脑 Rolandic 皮层回路，其结构及功能连接均存在异常，Emily 等人观察到，不同于健康儿童丘脑 Rolandic 皮层回路结构连接随着年龄增长而增加，较小年龄段 SeLECTS 患者其结构连接有异常增加，随着年龄增加结构连接相对减少，由此提出异常增加的结构连接可能涉及 SeLECTS 的发病，而后续连接减少可能是一种代偿机制[8]。同样的 Hunki Kwon 等人对比了疾病活动期、缓解期的 SeLECTS 患者及健康儿童的丘脑 Rolandic 皮层结构及功能网络连接，发现无论在疾病活动期还是缓解后的患者中，结构及功能连接与年龄的正相关均遭到破坏，并进一步将丘脑 Rolandic 回路异常定位到 Rolandic 下皮层－外侧核丘脑运动回路，其功能连接在 SeLECTS 疾病活动期患者中随着年龄出现异常增加，且可随着症状的缓解而缓解，但缓解后其结构连接呈异常增加[9]。基于 MRI 的形态学研究还发现 SeLECTS 患者中存在灰质异常增厚，主要集中在 Rolandic 区及涉及执行功能的区域，年龄越小越明显，随着癫痫病程的延长，皮层厚度可逐渐变薄[10]，符合其病程自限性特点，YinXu 等人的研究对比是否接受药物治疗的 SeLECTS 患者，发现使用药物治疗的患者其皮层厚度较未接收药物治疗的患者变薄，同时治疗后的患者较治疗前相应区域的皮层更薄，表明皮层形态改变可能在抗发作药物治疗中起到中介作用。

SeLECTS 患者合并的认知及行为障碍可能与中央颞区棘波(Centrotemporal spikes, CTS)密切相关，在双胞胎试验中观察到，即使没有癫痫发作，仅监测到 CTS 也可表现出类似的认知障碍及神经心理异常，同时注意缺陷及多动障碍(Attention deficit and hyperactivity disorder, ADHD)、孤独症谱系障碍(Autism Spectrum Disorder, ASD)等患者中 CTS 发生率远高于健康儿童中发病率。其机制可能与 CTS 干扰慢波及纺锤波的形成有关，后者对于记忆巩固及大脑突触可塑性至关重要，可进一步导致认知受损[11]，在合并 ESES 的患者中尤为显著[12]，但这种纺锤波缺陷仅在疾病的活动期短暂存在[11]。另外，CTS 还可影响正常的灰质修剪过程，使得本应消除的连接保留或建立异常连接，这对于执行功能影响尤为突出，涉及多种技能发展[13]。此外神经功能影像学发现致痫区的皮质存在代谢亢进，而病灶周围及远端的局部皮质存在代谢低下、功能连接减少，由此提出周围皮层抑制学说，认为这种代谢减低的皮质涉及到默认模式网络(default mode network, DMN)，这可能是影响认知的机制之一[14]。

3. SeLECTS 的共患病

在 SeLECTS 患者可合并一系列精神行为并发症[2]，最常见的为 ADHD，目前报道的共患率在29%~65.6%之间不等[15]，均远高于儿童中 7%~8%的患病率，共患 ADHD 的 SeLECTS 患者表现以注意力缺陷为主，且起病年龄越小的患者，注意力缺陷更严重[16]，共患 ADHD 的儿童在智力、语言等方面得分低于正常儿童；且较无相关合并症的 SeLECTS 患者病程更长，更倾向于接受多种抗发作药物治疗[17]，但随着病情缓解，注意力网络受损等可逆转[18]。其次抑郁焦虑等情绪障碍在 SeLECTS 患者中也较为常见，发生率约为 23.6% [2]，情绪障碍可能与年龄、放电指数及发作频率相关[19]。另有小部分患者还可合并孤独症谱系障碍、对立违抗性障碍等[15]。这些精神行为合并症在疾病活动期对于患儿技能学习、社交等方面有不同程度的影响，虽然研究报道在长期随访中对成年后生活质量无显著影响，但鉴于患者多处于学龄前及学龄期，仍有必要进行积极干预[20]。

一项大型 META 分析报道 SeLECTS 患者存在广泛的认知功能受损[21]，尤其是长期存储及获取能力缺陷，涉及将新信息进行储存和固化为长期记忆的能力，以及后续通过联想获取已经存储的信息，其次整体智能、获得知识、短期记忆能力、处理速度和流利程度－获取均有中等程度的受损，视觉信息处理能力则存在轻度受损。这些认知缺陷在 SeLECTS 患者中可表现为不同程度的语言障碍如语言表达能力，语言流畅度、语音意识、阅读能力等[22]，以及其他非语言认知功能如视觉整合能力、执行功能、精细动作执行、记忆和处理速度等；进一步可损害 SeLECTS 患者的社会认知能力，影响患者日常沟通及人际关

系的处理[23]，同时 SeLECTS 患者对于悲伤、恐惧和厌恶的情绪识别能力得分显著低于健康儿童，起病年龄越小这种差异越明显[24]。这些认知缺陷的发生多认为与发作频率、脑电图等临床特征无显著相关[23]，意味着即使在癫痫发作罕见或得到控制的患者，进行认知评估也很有必要。

4. SeLECTS 药物治疗反应及药物选择

SeLECTS 的发作稀疏及自限性病程为是否启用药物治疗带来争议，研究表明抗发作药物对于 SeLECTS 患者控制癫痫发作疗效十分有限，约三分之二患者在用药后仍有至少一次癫痫发作，即使达到连续 12 月无发作，仍有 38.3%患者后续再次发作[25]，且与未接受药物治疗的 SeLECTS 患者相比，药物治疗仅在最初 1~2 年内可显著减少发作频次[4]，接受药物治疗还会增加患者自卑、焦虑、抑郁及病耻感等，对其社交及自身发展造成影响[26]，部分药物如卡马西平、奥卡西平甚至可能加重病情、诱导其他形式发作、加重认知障碍等，故在衡量是否启用药物治疗及选用治疗方案时，应综合考量利弊。通常认为癫痫发作次数少、仅在夜间发作及年龄接近自然缓解的患者，一般不需要抗发作药物治疗，而有癫痫频繁发作、日间发作、出现继发性全身性发作，合并与 SeLECTS 相关的精神行为异常及认知障碍，以及出现睡眠中的癫痫电状态((ESES)等脑电图恶化趋势时应考虑开始药物治疗[27]。

关于抗发作药物的选择目前仍然缺乏可靠证据，2013 年 IALE 提出的 SeLECTS 的用药指南中推荐证据仅为 C 级(CBZ, VPA)、D 级(GBP, LEV, OXC, STM) [28]；不同国家地区用药方案有很大差异，2021 年英国国家卫生与临床优化研究所推荐的一线药物为 CBZ、LTG，2020 的比利时癫痫指南中推荐 VPA、LEV、sulthiame 作为首选[29]，国内专家共识则推荐 OXC 作为一线用药。国内临床最常用的抗发作药物是 OXC、LEV 及 VPA [3]。上述抗发作药物在癫痫发作结局上无显著差异，实际临床决策中需同时参考各类药物的安全性、耐受性及对神经心理等问题的改善作用等。

5. 研究展望

近年来基因测序及大脑功能影像学等检测手段为进一步探讨 SeLECTS 发病机制等提供了便利，还需更多研究进一步阐明，未来对于 SeLECTS 的遗传机制可能需要更多的多基因分析及表观遗传的研究，同时 SeLECTS 患者广泛合并的神经心理异常及认知障碍可能与其临床特征无关，故临床中应重视其心理及认知功能的评估，对于提升患者生活质量至关重要；另外目前抗发作药物治疗仍疗效有限，尤其对于有非典型进展的患者，需要更多临床研究协助用药方案的制定。

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