

儿童癫痫患者抗发作药物治疗与药物难治性癫痫的研究进展

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摘要

抗发作药物(antiseizure medications, ASMs)是儿童癫痫的一线治疗方法, 但其疗效存在高度异质性。多数患儿经治疗后最终可实现长期无发作, 然而, 不同癫痫类型、病因及综合征间的缓解率差异显著, 尤其以发育性癫痫性脑病(epileptic encephalopathies, DEEs)患者的预后最差。国际抗癫痫联盟(International League Against Epilepsy, ILAE)提出的药物难治性癫痫(drug-resistant epilepsy, DRE)定义是临床与研究的重要工具, 但其在儿童患者中的直接适用性存疑, 主要源于儿童癫痫病因、综合征等方面的特殊性。本综述旨在系统阐述儿童癫痫ASMs治疗结局的整体特征、异质性表现以及DRE的危险因素, 并探讨现有评估工具在儿科领域的适用性争议与未来方向。

关键词

儿童癫痫, 抗发作药物, 药物难治性癫痫

Research Progress on Antiseizure Medication Therapy and Drug-Resistant Epilepsy in Pediatric Patients with Epilepsy

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Abstract

In pediatric epilepsy, antiseizure medications (ASMs) are employed as the first-line therapeutic

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approach, yet their efficacy demonstrates substantial heterogeneity. While most children ultimately achieve long-term seizure freedom following treatment, remission rates vary significantly across different epilepsy types, etiologies, and syndromes, with the poorest prognosis observed particularly in patients with developmental epileptic encephalopathies (DEEs). The definition of drug-resistant epilepsy (DRE) proposed by the International League Against Epilepsy (ILAE) is an essential tool for both clinical practice and research; however, its direct applicability to pediatric patients remains questionable, primarily owing to the distinct characteristics of childhood epilepsy in terms of etiology and syndrome classification. This review aims to systematically elaborate on the overall features and heterogeneous outcomes of ASM treatment in pediatric epilepsy, identify risk factors associated with DRE, and discuss existing controversies regarding the applicability of current assessment tools in the pediatric field, along with future directions.

Keywords

Pediatric Epilepsy, Antiseizure Medications, Drug-Resistant Epilepsy

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1. 引言

癫痫是儿童期最常见的严重神经系统疾病之一, 全球疾病负担显著。其发病率和患病率因地区、年龄和研究方法而异。系统综述显示, 0~18 岁儿童癫痫发病率约为 46.9~85.29/10 万人年, 活动性癫痫的点患病率约为 6.38/千人[1]。年龄分布不均, 婴儿期(<1 岁)发病率最高[2], 最新研究进一步证实了高收入国家中儿童癫痫的持续疾病负担[3]。

ASMs 是儿童癫痫的一线治疗方法, 其核心目标在于预防癫痫发作复发[4]。然而, 儿童癫痫具有高度的异质性, 远非单一疾病[5]。病因学上, 约半数病例可归因于已知病因, 主要包括结构性(21%)和遗传性(33%), 而感染、代谢、免疫等因素则相对少见[3]。基于起病年龄、发作类型、脑电图等特征划分的癫痫综合征, 其临床表现、治疗反应及远期预后差异巨大[4]。其中, 自限性癫痫药物治疗反应良好, 单药治疗常可有效控制发作, 甚至存在自发缓解可能[6]。而 DEE 则是一类以癫痫发作、频繁癫痫样放电伴随发育迟缓或倒退为特征的严重疾病群体, 预后通常较差[7]。正是这种病因与综合征的多样性, 直接导致了 ASMs 治疗结局的显著差异。

ILAE 于 2010 年提出的 DRE 定义是癫痫管理领域的重要里程碑。其核心定义是: 在使用两种恰当选择、足量应用且耐受良好的 ASMs 方案(无论是单药或联合治疗)后, 仍未能实现持续无发作[8]。这一定义旨在标准化临床实践与研究, 促进难治病例的早期识别与转诊, 但鉴于儿童癫痫患者在病因、综合征及发育阶段等方面的高度异质性, 其在儿童群体中的直接应用仍存在显著局限性与争议。

下文将先总结 ASMs 治疗结局的特征与异质性, 再分析 DRE 的发病特点与危险因素, 最后探讨现行标准的局限与未来方向。

2. 儿童癫痫 ASMs 治疗结局

2.1. 治疗反应的动态演变

长期随访研究表明, 大多数儿童癫痫患者最终能够实现长期无发作, 总体结局乐观。一项超长期前瞻性研究显示, 至末次随访时, 64%的存活患者实现了至少 5 年无发作, 其中近半数已成功停药[9]。这

一趋势在最新的大型队列研究中得到印证, 约 78% 的儿童期起病患者在中位随访 10.6 年后达到至少 1 年无发作[10]。然而, 儿童癫痫的病程常呈动态变化, 表现为发作类型的演变或“缓解-复发”模式, 这使得“持续无发作”状态的判断趋于复杂[11]-[13]。因此, 治疗结局的评估需置于一个动态且长期的框架中进行[14]。

2.2. 治疗结局的异质性

抗发作药物治疗结局在不同发作类型、病因和综合征之间存在显著差异。

局灶性癫痫的发作控制率(84%)通常高于全面性癫痫(75%), 而兼具两者特征的癫痫类型预后极差(26%) [10]。

在病因层面, 未知病因的癫痫预后最佳(89%无发作), 而明确的结构性(58%)或遗传性(54%)病因则与较低的缓解率显著相关[2] [10]。

综合征诊断能直接体现预后差异[15]。自限性癫痫综合征(如伴中央颞区棘波的儿童自限性癫痫)和儿童失神癫痫代表了预后最佳的群体, 无发作率可高达 96%~98% [10]。相反, 大多数 DEEs, 如 Dravet 综合征、Lennox-Gastaut 综合征(LGS), 其无发作率极低(0%~53%), 且常伴有严重的神经发育共病[7] [10]。青少年肌阵挛癫痫等特发性全面性癫痫的预后则介于两者之间。

3. 药物难治性癫痫

3.1. 流行病学特征

DRE 在儿童癫痫中的比例因研究群体及采用的诊断标准而异[16]。总体上, 约 25%符合药物难治性癫痫标准[16]。然而, 不同综合征间的差异巨大: 例如, LGS 的难治比例可高达 79.0%, 而儿童失神癫痫仅为 7.1% [17]。一项为期 15 年的随访研究显示, 约 12.1%的患儿会经历一段难治期, 其中部分为暂时性, 最终仍有 8.5%持续为难治[18]。

3.2. 危险因素

DRE 的发生是多种因素共同作用的结果, 早期识别其危险因素对于优化治疗策略、改善患儿预后至关重要[19], 基于现有证据, 其主要危险因素可归纳如下。

3.2.1. 病因与综合征

多项研究证实, 明确的病因(尤其是结构性、遗传性)是 DRE 最强的独立预测因素[19]-[21]。从病理生理机制来看, 遗传性病因常导致广泛的、根本性的神经元功能障碍, 且这类病因与 DEE 高度重叠, 直接决定了其严峻的治疗预后[4]; 而结构性病因则意味着脑内存在持续诱发异常放电的致病病灶, 由此引发的全脑网络功能障碍往往呈进行性加重趋势, 常规 ASMs 难以从根源上消除这一病理基础[22]。值得注意的是, DEEs 本身即代表了一类起病即高度难治的特殊群体[10], 如 Dravet 综合征、Lennox-Gastaut 综合征(LGS)和 West 综合征等, 均与 DRE 存在高度关联性[23] [24]。这些综合征通常具有特定的基因突变背景, 例如 Dravet 综合征常与 SCN1A 基因变异有关[25], 这也进一步解释了其对 ASMs 治疗反应不佳的核心原因。

3.2.2. 临床发作特征

婴儿期发病, 尤其是出现癫痫性痉挛, 是预示高风险的信号[20] [26]。而 5~9 岁起病则常与较好的预后相关[27]。此外, 初始发作频率高、存在多种发作类型、有癫痫持续状态病史, 均提示药物难治风险增加[27] [28]。

3.2.3. 早期治疗反应

早期治疗反应是预测远期疗效的重要指标。2000年一项前瞻性研究对新诊断的癫痫患者进行长期随访发现,在接受第一种ASM治疗后,约47%的患者实现发作控制;而初始治疗无效的患者中,即使更换第二种药物,仅约13%获得缓解。若两种ASMs治疗均失败,后续发展为DRE的概率则显著升高至约80%[29]。这表明,初始抗癫痫药物治疗无效,不仅意味着当前治疗方案的失败,更是该癫痫类型可能具备“内在严重性”的有力提示。其背后的病理生理机制,可能与在疾病早期即已启动的、多重交互的耐药通路有关,包括但不限于药物作用靶点的功能改变、多药转运蛋白的过度表达、异常的神经网络重构以及慢性的神经炎症过程[30]。

3.2.4. 神经发育情况

智力障碍或发育迟缓是药物难治性癫痫的显著预测因子[19][31]。异常的神经发育状态往往提示存在潜在的、严重的脑结构性或功能性异常。

上述因素可作为临床早期识别DRE高危患儿的核心指标,对存在相关危险因素的患儿启动更密切的随访与多学科评估,以避免延误干预时机。

3.3. 现行标准的局限性

尽管ILAE的DRE定义为临床提供了重要框架,但其在儿童癫痫中的直接应用仍存在显著局限性与争议。首先,儿童癫痫,特别是DEE,具有与成人迥异的病因谱和病理生理机制。许多综合征在起病初期即表现为高度难治,若严格等待“两种抗发作药物失败”可能延误早期、积极的干预时机,错过神经保护的关键窗口[11][30]。其次,儿童大脑处于快速发育期,药物代谢、受体分布及神经网络可塑性不断变化,导致药物反应模式更动态,因此基于固定药物试验次数的“耐药”判断可能无法准确反映疾病本质[11][32]。最后,定义中“无发作”的时限(如12个月)对于某些严重、发作频繁的儿童癫痫类型可能缺乏临床意义,同时,单纯以“无发作”为终极目标,可能忽略了发作频率降低或严重性减轻等部分治疗反应对患儿生活质量及发育结局的积极价值[11]。最后,在当前精准医疗快速发展的时代背景下,儿童癫痫的治疗范式正经历深刻转变,其核心已从传统、经验性的ASMs,转向基于特定病因与靶向病理生理机制的新策略[33]。尽管目前许多方法仍处于前沿探索或早期应用阶段,这种治疗范式的演进,使得现有的DRE定义,面临重新审视与更新的迫切需求[34][35]。

3.4. 未来展望

鉴于上述挑战,国际学界正积极推动建立更符合儿童癫痫特征的评估框架。最新共识呼吁制定儿童特异性的、更具动态性和机制导向的定义[11][30]。未来的方向包括:

- 1) 整合综合征与病因信息:在诊断早期即结合特定综合征(如DEEs)和明确的高危病因(如某些基因突变),允许更早地启动“可能难治性”评估和综合管理方案[36]。
- 2) 采用分层或时间敏感性定义:根据年龄和综合征调整判断阈值,例如对某些DEE可考虑“一种适当药物治疗失败后”即启动难治性评估流程。
- 3) 探索多元生物标志物:结合遗传学、神经影像学 and 脑电等多模态生物标志物,建立超越单纯临床发作的客观预测模型,实现更早期的精准识别。

4. 总结

儿童癫痫的ASMs治疗结局整体乐观,但异质性极高,从根本上取决于癫痫的具体类型、病因和综合征。ILAE的DRE定义是识别和管理高风险患儿的重要工具,但其在儿科的应用需审慎。当前,基于

成人经验的标准未能充分涵盖儿童癫痫的发育动态性和特殊综合征的早期难治性。一项针对成年患者的长达 30 年的纵向队列研究显示, 新型药物广泛应用后, 实现无发作的患者比例并没有增加[37], 但新型抗癫痫药物对于儿童癫痫患儿预后的影响目前还缺乏临床证据[35]。未来的研究和临床实践应致力于发展并验证适用于儿童群体的, 整合了病因、综合征及发育阶段的多维评估体系, 以推动早期识别、实施个体化干预并改善远期神经发育结局, 真正实现从“控制发作”到“优化整体生命轨迹”的诊疗目标。

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