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Hans汉斯

儿童耐药癫痫的早期手术治疗研究进展

文世行[1]，张　璇[2*]

[1]济宁医学院临床医学院，山东　济宁
[2]济宁市第一人民医院神经内科，山东　济宁

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摘　要

癫痫是一种由多病因引起的脑部慢性疾病，以神经元过度放电导致反复性、发作性和短暂性的中枢神经系统功能失常为特征。多数患者在儿童期发病，并逐渐进展为耐药性癫痫，对患儿的智力造成极大的损伤，对患儿的生存能力造成了极大的危害，极大地降低了患儿的后期生活质量。对于耐药的儿童癫痫患者的外科治疗近些年技术发展迅速，疗效优于一般的药物治疗，但早期手术治疗的患者很少。本文主要就儿童耐药癫痫的早期手术治疗方式和效果方面来进行简要综述。

关键词

耐药癫痫，儿童，手术，治疗

Advances in Early Surgical Treatment of Drug-Resistant Epilepsy in Children

Shihang Wen[1], Xuan Zhang[2*]

[1]Clinical Medical College of Jining Medical University, Jining Shandong
[2]Department of Neurology, Jining First People's Hospital, Jining Shandong

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Abstract

Epilepsy is a chronic brain disease caused by multiple causes, characterized by recurrent, paroxysmal and transient central nervous system dysfunction caused by excessive discharge of neurons. Most patients develop in childhood and gradually develop into drug-resistant epilepsy, which does great harm to the quality of life of the patients. The surgical treatment of drug-resistant children with epilepsy has developed rapidly in recent years, and the curative effect is better than that of

*通讯作者。

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general drug treatment, but the use is still not common enough, and there are few patients with early surgical treatment. This article mainly reviews the early surgical treatment of drug-resistant epilepsy in children.

Keywords

Drug-Resistant Epilepsy, Children, Surgery, Therapy

1. 引言

癫痫是最常见的神经系统疾病之一，可以影响所有年龄、种族、社会阶层的人。癫痫可造成患者的神经生物学、认知和心理改变[1]。癫痫是儿童时期最常见的慢性神经系统疾病[2]。在儿童中，癫痫发生在大约 1%的人口中，药物治疗是一线治疗，但仅靠药物治疗仍不能充分控制癫痫发作[3]。约有 20%的儿童出现耐药癫痫(drug resistant epilepsy, DRE) [4]，此时就需要进行外科手术治疗来治愈或缓解癫痫症状，但是大部分的患者并没有在疾病的早期进行及时有效的手术治疗。本文主要就耐药癫痫患者的早期手术治疗进行简要概述，对往后关于这方面的实验研究提供一种可能的方向和临床治疗选择术式提供一种可能的选项。

2. 耐药癫痫

癫痫最常发生在儿童早期，经常伴随着认知、行为和精神方面的共病，在成年后会产生毁灭性的影响[5]。DRE 指正确选择至少 2 种可耐受的抗癫痫药单药或联用，经足够的剂量和疗程后，患者在治疗前最长发作间隔的 3 倍或 1 年(取决于两者之间何者更长)的时间内仍发作[6]。最近的一项荟萃分析表明癫痫患者 DRE 的总患病率为 30% (95%CI 为 0.19~0.42)，合并发病率为 15% (95%CI 为 0.11~0.19) [7]。DRE 导致患者生活质量下降，智力、工作和记忆能力显著下降，过早死亡的风险增加，抑郁和焦虑等精神疾病的风险增加[4]。有关的研究表明耐药性患者的猝死发生率更高[8]。然而，最近的荟萃分析表明大约三分之二的 DRE 儿童通过精心选择的癫痫手术，可以使癫痫发作缓解或显著(>90%)减少癫痫发作[9]。儿童可手术治疗的癫痫应及早发现，手术应该作为一种选择，而不是作为最后的治疗手段[9]。

3. 耐药机制

难治性癫痫的耐药机制并不完全清楚，没有统一的结论[10]。但是国内外的研究假设表示大多与神经网络以及环路的重组[11]，海马硬化[12]，突触囊泡，网格蛋白，离子通道的改变[13]，以及多药耐药基因的表达[14]有关。

4. 癫痫的手术治疗

早在 1909 年国际抗癫痫联盟第一次会议召开时，手术治疗癫痫就已有 20 多年历史，但很少被医生使用。在 1992 年的第二次棕榈滩会议，癫痫手术被接受为耐药局灶性癫痫的标准治疗方法，并在国际癫痫学会大会中得到很好的代表[15]。癫痫外科手术治疗以下原因引起的癫痫：对抗癫痫药物有抵抗力的癫痫发作；通过药物控制但无法忍受副作用为代价的癫痫发作；尚未被定义为耐药的癫痫发作，但与结构

性损害有关，几乎总是产生耐药性或迫使患者接受药物治疗[16]。当癫痫的病因与局限的结构性病变有关时，手术在选定的病例中可以是“治愈的”[17]，如局灶性皮质发育不良 II 型和神经胶质瘤，组织病理学特征明确，手术后的预后良好[18]。随着激光消融和姑息性神经调节方法的引入，极大地增加了可以从手术中受益的患者人数。然而，这种替代疗法仍然没有得到充分利用，只有不到 1%的潜在患者被转诊到癫痫中心进行手术治疗[15]。

5. 手术方式和疗效

手术方式选择包括切除手术(病变切除、脑叶切除、多叶切除)，微创手术[激光间质热疗术(laser interstitial thermal therapy, LITT)、聚焦超声术(focused ultrasound, FUS)]，姑息性的外科手术包括脑深部刺激术(deep brain stimulation, DBS)、迷走神经刺激术(vagus nerve stimulation, VNS)、反应性神经刺激术(responsive neurostimulation, RNS)和立体脑电(stereo-electro-encephalography, SEEG)引导下的射频热凝术(the radiofrequency thermocoagulation, RF-TC)。

5.1. 颞叶切除术

颞叶切除术包括前颞叶切除术，海马切除术，杏仁核切除术等术式。对大多数耐药的颞叶癫痫患者可以在没有侵入性的术前脑电检查的情况下接受手术。当放射或电临床检查显示病变区域涉及新皮质的患者中，最好的治疗方法是同时切除新皮质和内侧颞叶结构[19]。最近的荟萃分析和不同的病例系列报道了在颞叶切除术后类似的结果，65%~69%的患者没有癫痫发作[20] [21]。

5.2. 大脑半球切开术

大脑半球切开术是治疗一侧半球性癫痫的手术方式之一，通常适用于弥漫性损伤、存在明显的运动障碍和偏侧大脑半球的癫痫发作活动的患者。术式包括经旁矢状面大脑半球切开和岛周大脑半球切开等多种方式[22] [23]。该术式完全离断整个大脑半球而不做皮质切除,比功能性大脑半球切除术的效果更令人满意[24]。相关的研究报道表明接受治疗的患者癫痫无发作的比率大于 75% [25]。

5.3. 脑深部刺激术

DBS 是刺激丘脑前核治疗癫痫，可能与丘脑前核和边缘系统之间的联系有关，这种开环装置在颞叶癫痫和意识受损的局灶性癫痫发作中似乎特别有效，这表明它可能在癫痫发作传播方式发挥重要作用[26]。DBS 是一种安全有效的治疗方法，尤其是对难治性部分性发作患者(四分之三的患者 5 年后发作减少至少 50%) [27]。

5.4. 聚焦超声术

自 20 世纪 40 年代以来，FUS 一直被研究用于神经外科[28]。近年来，FUS 已成功应用于治疗特发性震颤、帕金森病、神经病理性疼痛、抑郁症和强迫症[29] [30] [31] [32]。FUS 可以以局部、短暂、无创的方式打开血脑屏障，这可能被证明对癫痫、肿瘤、阿尔茨海默病或其他疾病的治疗有用，甚至有助于液体活组织检查[28]。

5.5. 激光间质热疗术

近些年随着微创技术的发展，皮质发育畸形的癫痫患者可进行在脑磁共振引导下行激光间质热疗术，此术式在此类儿童癫痫患者中具有显著的潜力，可以作为更传统技术的微创和成本效益的替代方案。LITT 优点包括较低的手术发病率、较小的切口、较短的住院时间、较少的出血量和较少的术后疼痛[33]。与其

他微创技术相比，LITT 具有明显的优势，包括实时图像引导，潜在的更大消融量，以及具有延迟风险的即时治疗效果[34]。

5.6. 反应性神经刺激术

RNS 是一种创新的闭环系统，用于治疗伴有致残性发作(即局灶性运动、局灶性意识障碍、局灶性至双侧强直–阵挛)的抗药性癫痫和发作灶不超过 2 个的患者或双侧颞叶癫痫患者。然而，因为 RNS 需要初步的侵入性脑电检查来检测发作起始区，同时还需要开颅手术更换电池，还需要定期上传数据，患者的依从性不佳[17]。但 RNS 支持长期的脑电监测，可提供大量有价值的信息，在研究和临床实践中都具有潜在的积极意义[35]。

5.7. 迷走神经刺激术

植入迷走神经刺激器显著改善了有或没有接受癫痫手术的儿童的癫痫发作频率。VNS 被认为是既往手术失败的儿科患者的一种替代疗法，是治疗耐药癫痫患者的一种非药理学方法。对于不适合癫痫手术的患者，VNS 提供了另一种有效的癫痫控制方法。VNS 已被证明对局灶性、全身性和综合征形式的癫痫有效[36]。

5.8. 立体脑电引导下的射频热凝术

SEEG 引导下的 RF-TC 技术包括使用连接到 RF 发生器的立体植入电极来产生热损伤，目的是破坏在 MRI 上发现的致痫病变区域。对内侧颞叶癫痫、局灶性皮质发育不良和下丘脑错构瘤的治疗效果良好[37]。SEEG 引导的 RF-TC 最初是一种姑息治疗，大约一半的接受治疗的患者癫痫发作频率减少了 50% [38]。

6. 早期手术优势

癫痫手术的理想目标是在不引起神经系统并发症的情况下完全控制癫痫发作，从而避免癫痫持续发作和/或长期给予药物治疗的潜在长期后果。三项成人和一项儿童随机对照临床试验以及几项荟萃分析和系统评价证明了它在精心挑选的癫痫患者中的安全性和有效性大于药物治疗[39]。

顽固性癫痫手术是治疗婴儿和儿童耐药癫痫的一种可行的治疗方法，由于未成熟的大脑比成熟的大脑更具可塑性，早期接受手术治疗的患者的临床和神经发育结果更好[40]。现有数据表明，儿童出现严重的难治性可定位的癫痫，都应考虑进行手术评估致痫区域，移除该区域将导致无癫痫状态[41]。癫痫手术后注意缺陷多动障碍和 ASD 症状明显改善。提高了患者的事物应对技能和社区技能，改善了患者的适应行为[42]。这些症状的改善都有助于患者日后的疾病恢复，可以最大程度保证患者的身心健康和社会生存技能的改善。此外，随着手术技术、围手术期麻醉、重症监护和经验的改进，儿科癫痫手术围手术期的发病率和死亡率显著降低，癫痫手术成为儿童 DRE 早期可接受的治疗选择[43]。

7. 总结与展望

DRE 的患儿进行早期的癫痫手术可以获得良好的预后，而且患者后期的治疗费用也可以大幅下降。此外，随着结构和功能神经成像和脑电视频监测技术的进步，加上侵入性电极植入技术的简化和新神经外科工具的出现，拓宽了手术的适应症，同时使手术变得更安全和更少侵入性。早期进行手术可获得良好的获益，但对于早期癫痫患儿手术的适应症拓展现在仍缺乏大量的相关研究文章。

利益冲突声明

所有作者无利益冲突。

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