



电子、语音版

·综述·

海马硬化所致耐药性癫痫外科干预的研究进展

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摘要: 海马硬化是耐药性癫痫的主要病理基础。近年来, 外科手术在精准化、微创化和个体化方向取得显著突破。该文系统综述了传统术式前颞叶切除术与选择性杏仁核-海马切除术及新技术激光间质热疗、射频热凝等在海马硬化所致耐药性癫痫方面的研究, 以期海马硬化所致耐药性癫痫外科干预的预后影响因素和未来发展方向提供参考。

关键词: 海马硬化; 耐药性癫痫; 难治性癫痫; 激光间质热疗; 射频热凝; 神经调控

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Research advances in surgical intervention for drug-resistant epilepsy caused by hippocampal sclerosis

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Abstract: Hippocampal sclerosis is the main pathological basis for drug-resistant epilepsy. In recent years, remarkable breakthroughs have been achieved in surgical interventions in terms of precision, minimally invasive techniques, and individualized treatment approaches. This article systematically reviews the research advances in traditional surgical procedures (anterior temporal lobectomy and selective amygdalohippocampectomy) and new techniques (laser interstitial thermal therapy and radiofrequency thermocoagulation) in the treatment of drug-resistant epilepsy, in order to provide a reference for determining the influencing factors for prognosis after surgical intervention for drug-resistant epilepsy and future research directions.

Keywords: hippocampal sclerosis; drug-resistant epilepsy; intractable epilepsy; laser interstitial thermal therapy; radiofrequency thermocoagulation; neuromodulation

耐药性癫痫(drug-resistant epilepsy, DRE)指经过两种或两种以上的抗癫痫药物治疗后, 仍然无法控制癫痫发作的情况^[1]。研究发现, DRE与海马硬化(hippocampal sclerosis, HS)密切相关^[2-3]。HS是导致DRE的重要病理基础, 特别是在颞叶癫痫中, 其发生率高达60%至80%^[4]。尽管药物治疗是癫痫的首选治疗方法, 但对于大多数DRE患者, 特别是伴有HS的患者, 外科手术可以显

著改善其临床预后。研究显示, 接受外科手术的大部分患者能够实现发作控制, 且术后认知功能也有明显改善^[5]。总的来说, 针对DRE的外科干预在改善患者的生活质量和控制癫痫发作方面具有重要意义。

1 HS的病因及其与癫痫的关系

1.1 HS的形成机制

HS是DRE特别是内侧颞叶癫痫的常见病理基础^[6]。

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其形成机制通常与早期脑组织损伤有关,如高热惊厥、颅内感染、缺氧或外伤等,这些事件被称为初始诱发事件^[7-9]。研究表明,HS主要是由于海马CA1、CA3区锥体神经元选择性凋亡和反应性星形胶质细胞增生所致^[10]。感染或自身免疫反应引发胶质细胞增生(尤其是星形胶质细胞和小胶质细胞活化)^[11],活化的胶质细胞释放大炎症因子[如白细胞介素-1 β (Interleukin-1 β , IL-1 β)、肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)],形成神经炎症级联反应,进一步破坏血脑屏障,促进外周免疫细胞浸润,加剧神经元损伤。同时,遗传因素[如电压门控钠离子通道 α 亚基1(SCN1A)基因突变]和表观遗传调控异常(如DNA甲基化失衡)可能影响离子通道功能,导致离子通道异常(如钠、钙通道失调)和递质与神经肽失调[谷氨酸过度释放、 γ -氨基丁酸(γ -aminobutyric acid, GABA)能抑制减弱],使神经元兴奋性失控^[12]。随着病理进展,海马区发生结构重构:齿状回颗粒细胞的轴突异常增生形成异常神经网络(如苔藓纤维发芽),并与海马-边缘系统环路异常联动,破坏正常信息传递。这种突触重

塑与胶质瘢痕共同促进癫痫发作的易感性。此外,持续的炎症和代谢紊乱(如线粒体功能障碍)形成正反馈循环,最终导致海马组织硬化^[13]。这一过程不仅涉及局部病理改变,还可能通过异常神经振荡影响全脑网络,成为DRE的核心机制。

1.2 HS与癫痫发作的相关性

HS通常表现为海马区域神经元的丧失和胶质细胞的增生,这种病理变化可能是癫痫发作的核心机制之一。神经元选择性丧失触发胶质细胞活化^[14],释放IL-1 β 、TNF- α 等炎症因子,引发神经炎症级联反应并破坏血脑屏障,促使外周免疫细胞浸润加重损伤;同时,结构重构形成异常神经网络,与海马-边缘系统环路的紊乱协同,导致神经元同步化放电^[15-16];离子通道异常和递质与神经肽失调进一步打破兴奋-抑制平衡,而遗传与表观遗传调控巩固致痫网络^[17-18];反复癫痫发作通过钙超载、氧化应激及线粒体功能障碍形成“损伤-放电-再损伤”恶性循环,最终导致海马不可逆硬化及耐药性颞叶癫痫^[19](见图1)。

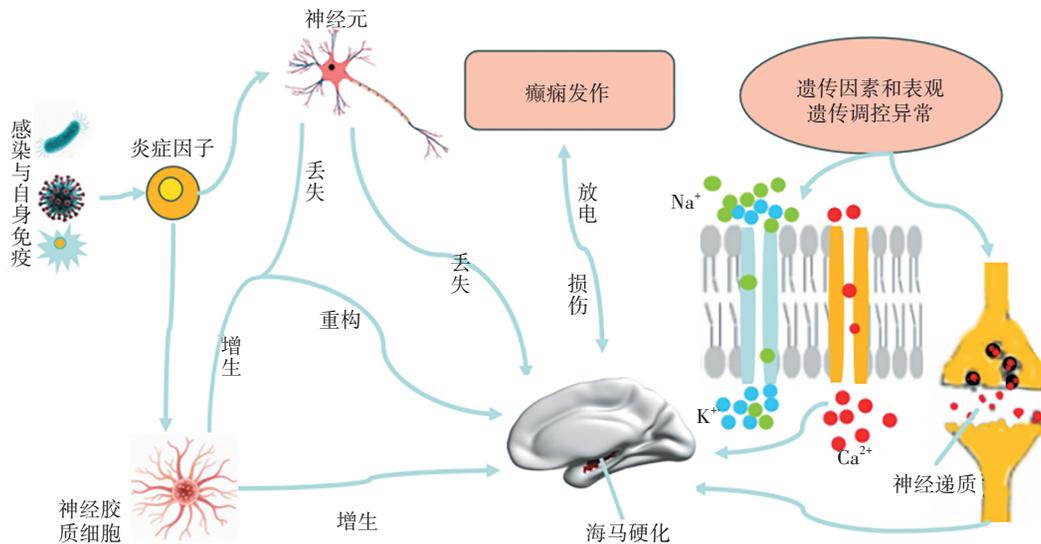


图1 HS形成机制及与癫痫发作的相关性

2 外科手术适应证的评估

2.1 HS影像学的评估

影像学检查能够提供关于病变位置、大小和性质的关键信息^[20],在外科手术适应证的评估中发挥着至关重要的作用,尤其是在癫痫外科手术中。通过高分辨率的磁共振成像(magnetic resonance imaging, MRI)和计算机断层成像(computed tomography, CT)扫描可以准确识别HS的存在。借助影像学检查可发现HS最显著的特征是海马头部和体部的萎缩及灰质丧失^[21-22]。

2.2 临床评估标准

外科干预对于治疗HS引起的DRE是一个重要的选

择。临床评估的标准主要包括以下几个方面:①DRE的确认,即至少尝试过两种抗癫痫药物治疗后仍然无法控制癫痫发作^[23]。②MRI是评估HS的金标准,对于HS, MRI表现为海马的对称性萎缩和信号改变,这为外科干预提供了重要的证据^[22]。③单光子发射计算机断层摄影(SPECT)和正电子发射断层摄影(positron emission tomography, PET)常常作为额外的影像学工具,帮助进一步确认癫痫的发作起源,尤其是在影像学检查结果和临床症状之间存在矛盾时。这些工具对于定位癫痫致痫灶,特别是颞叶癫痫具有重要作用^[24]。④脑电图(Electroencephalography, EEG),通过EEG定位癫痫致痫

灶是外科评估的关键步骤。视频脑电图 (video-electroencephalography, vEEG) 监测有助于明确癫痫发作的起源区,并确认是否为海马区域的病变^[25]。⑤神经心理评估,术前神经心理学评估可以帮助预测患者手术后记忆功能的变化,研究发现,在HS患者中,术前记忆缺损可能导致术后认知功能进一步下降^[16]。

3 HS所致DRE的外科手术方法

前颞叶切除术 (anterior temporal lobectomy, ATL) 与选择性杏仁核-海马切除术 (selective amygdalohippocampectomy, SAH) 是治疗由HS引起DRE的两种常见外科手术方法,随着医学技术的飞速发展,一些新技术如激光间质热疗、射频热凝等微创技术以及神经调控技术也被应用于HS引起的DRE中(见图2及表1)。

3.1 ALT

ATL是治疗DRE的重要外科手术,尤其适用于颞叶癫痫患者。神经导航技术和术中电生理监测被广泛应用于ATL中,以确保切除的精确性和安全性。术中监测可以实时评估大脑功能,避免对重要功能区的损伤,从而降低术后并发症的风险;正确识别异常组织后,通常会选择切除包括海马体和杏仁体在内的相关结构,以最大限度地降低癫痫复发的风险。一项系统评价和荟萃分析发现ATL在治疗HS所致DRE的患者中,术后约50%的患者可实现长期无发作,表明手术对HS所致的DRE具有较高的治疗成功率^[26]。也有研究认为HS引起的药物抵抗性颞叶癫痫患者在接受手术治疗后,术后大约60%~80%的患者癫痫发作减少^[27]。研究表明,手术后大多数患者经历不同程度的记忆丧失,尤其是左侧颞叶切除的患者,同时,患者的语言记忆可能受损,手术后的情绪变化也是一

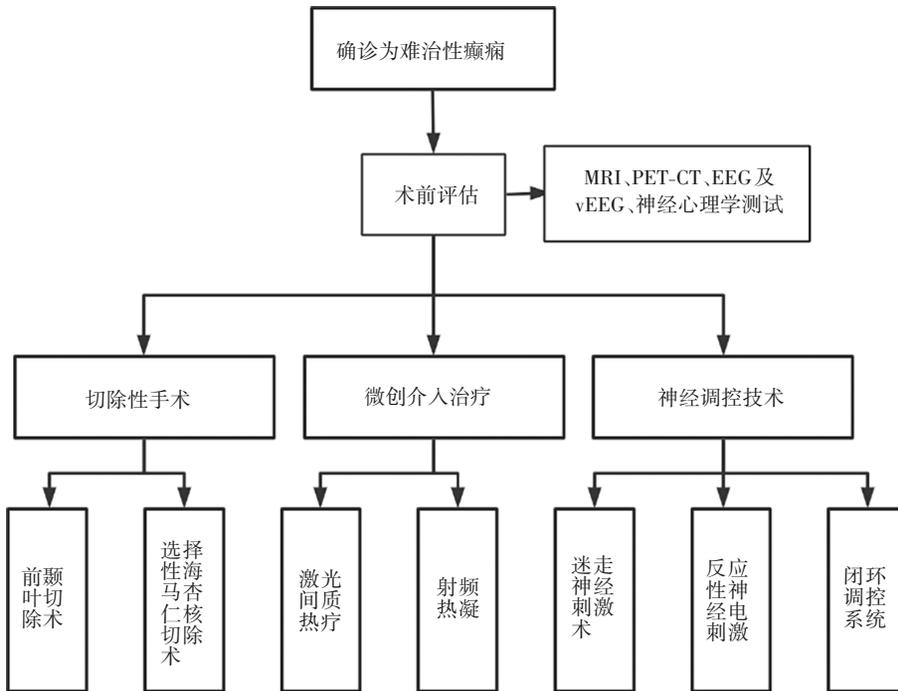


图2 HS所致DRE的外科手术治疗方案

表1 HS所致DRE的外科手术方法

手术方法	治疗效果	优势	最新进展
前颞叶切除术(ATL)	无发作率50%,减少发作率60%~80% ^[26-27]	高成功率;广泛适用性	传统主流术式,但功能损伤风险较高
选择性杏仁核-海马切除术(SAH)	癫痫控制效果显著,老年患者有效 ^[29-30]	认知功能影响较小;保留更多正常脑组织 ^[31]	对老年患者认知功能保护更优
激光间质热疗(LITT)	无发作率58%~72% ^[36]	功能保护(语言记忆提高15%~20%);适应双侧HS ^[4,37]	试验支持双侧HS治疗;AI优化消融参数 ^[4,35]
射频热凝(RFTC)	1年无发作率65.2% ^[41]	微创;儿童安全性高 ^[41]	支持双侧消融(≥60%体积);AI路径规划提升精度 ^[40,42]
神经调控技术(DBS、RNS)	DBS:5年无发作率54%;RNS:3年应答率68%;联合治疗无发作率71% ^[43,46,49]	非破坏性治疗;认知保护;实时癫痫网络干预 ^[47]	2024年光遗传+DBS联合疗法;闭环RNS灵敏度92% ^[44-45]

个常见的并发症,患者可能出现焦虑、抑郁或情感不稳定^[28]。

3.2 SAH

SAH手术包括以下2个关键步骤:①术中采用立体定向框架或现代神经导航系统确保对病变区域的精确定位;②根据术前影像和定位,海马和杏仁核的精准切除,使用神经电生理监测,以实时检查神经功能,防止不必要的损伤。研究发现,SAH术后大多数患者的癫痫症状得到了有效控制^[29]。一项针对年龄在50岁以上的HS患者的研究^[30]发现:接受SAH术后的癫痫发作显著减少,且手术对老年患者同样有效。而另一项研究^[31]评估了SAH对HS引起的DRE患者记忆和执行功能影响,发现该手术对患者的认知功能有较小的负面影响,且在控制癫痫发作方面非常有效。SAH术后患者可能出现焦虑、抑郁或情绪不稳定等症状,这与杏仁核和海马的切除有关^[27]。SAH术后可能影响到视觉区域,导致视野缺损或其他视方问题^[32]。

3.3 激光间质热疗

激光间质热疗(laser interstitial thermal therapy, LITT)通过MRI实时引导,将光纤探头精准植入海马致病病灶,利用980~1 064 nm激光的热效应选择性消融病变组织,同时保留周围正常的脑组织^[33]。近年来技术突破集中在:①多模态影像融合,集成弥散张量成像(DTI)与功能磁共振成像(fMRI)数据优化穿刺路径规划,避免损伤视辐射及语言功能区^[34];②动态温度监控,高场强(3T)磁共振温度成像可将温度分辨率提升至 $\pm 1^\circ\text{C}$,实现消融范围到达毫米级^[4];③人工智能辅助决策,基于深度学习的算法可预测热扩散模型,个体化设置能量参数(通常5~12 W,持续1~3 min)^[35]。多项前瞻性研究表明,LITT治疗HS致DRE的短期无发作率(Engel I级)达58%~72%,与传统前颞叶切除术相当,但住院时间缩短至1~2 d^[36]。其优势体现在:①功能保护,术后语言记忆评分比开颅手术提高15%~20% ($P<0.05$),尤其适用于优势半球病变^[37];②适应证扩展,2023年SANTE试验亚组分析证实,LITT对双侧HS患者仍能实现40%发作减少率^[4];③并发症发生率降低,系统性综述显示,永久性视野缺损发生率仅2.1%,低于开颅手术(8.7%)^[36]。

3.4 射频热凝

射频热凝(radiofrequency thermocoagulation, RFTC)通过电极针释放高频电流(460~500 kHz),靶向消融海马致病灶,核心技术创新包括:①多模态影像融合,结合7T MRI与DTI纤维追踪,穿刺精度提升至 $\pm 0.3\text{ mm}$,避免损伤视辐射及穹窿^[38];②实时温度反馈,新型热电偶探头可监测消融区温度(42~90 $^\circ\text{C}$),实现病灶范围动态调控(误差 $<1\text{ mm}$)^[39];③人工智能规划,基于深度学习的消融路径算法(如ResNet-50)可预测热扩散模型,个体化设定

能量参数(通常15~30 W,持续60~90 s)^[40]。国际多中心研究^[41]显示,RFTC治疗HS致DRE的术后1年Engel I级无发作率达65.2%,与传统ATL相当($P=0.34$),但语言记忆保留率提高28% ($P<0.01$)。其优势体现在:①微创性,平均住院时间缩短至2.1 d,并发症(如感染、脑水肿等)发生率降至3.5%^[4];②双侧HS适应证,2024年RCT研究表明,双侧海马消融(消融体积 $\geq 60\%$)可使发作频率减少 $\geq 50\%$ ^[42];③儿童患者安全性,针对儿童HS致DRE,术后认知发育评分(WISC-V)无下降($P=0.12$)^[42]。

3.5 神经调控技术

神经调控技术通过靶向干预癫痫网络,为海马HS所致DRE提供了非破坏性治疗选择。神经调控技术主要包括深部脑刺激(deep brain stimulation, DBS)、反应性神经刺激(responsive neurostimulation, RNS)及闭环调控系统。多中心研究证实,双侧前丘脑核DBS治疗HS致DRE的5年无发作率(Engel I级)达54%,优于传统单侧刺激(38%, $P=0.012$)^[43]。新型闭环RNS系统可实时监测海马theta振荡(4~8 Hz),发作预测灵敏度提升至92% (AUC=0.88),刺激响应时间缩短至0.2 s^[44]。有实验显示,海马CA1区光遗传刺激联合DBS可使癫痫发作频率降低76% ($P<0.001$)^[45]。并且队列研究($n=214$)表明,RNS治疗HS致DRE的3年应答率(发作减少 $\geq 50\%$)为68%,且术后语言记忆评分无下降($P=0.15$)^[46];低强度DBS(1.5~2.0 V)用于儿童HS致DRE,术后12个月认知发育指数(cognitive development index, CDI)提高12% ($P=0.03$)^[47];感染率(2.1%)与硬件故障率(1.8%)较早期技术下降60%^[48]。2023年临床试验显示,DBS联合海马高频振荡靶向消融可使无发作率提升至71%^[49]。

4 长期随访的重要性与策略

长期随访在术后管理中起着至关重要的作用。患者术后认知功能尤其是记忆、语言和执行功能的变化,是影响患者生活质量的关键因素之一。因此,术后定期实施心理评估是必不可少的环节。同时,术后患者的药物管理需要根据手术后的癫痫发作情况进行适时的调整。虽然手术能显著减少癫痫发作,但部分患者仍需长期服用抗癫痫药物以维持疗效。因此,药物的优化管理和逐步减少药物使用是随访中的重要环节。特别是在癫痫发作得到控制后,应考虑逐渐减药,避免因长期使用药物而引起的不良反应。

5 小结

HS所致DRE的外科干预,传统的前颞叶切除术和选择性杏仁核-海马切除术已被证明在改善患者癫痫控制方面具有显著疗效,但手术创口大,感染风险高,住院时间延长。新技术的发展可弥补以上不足,且多模态联合的手术方法可明显降低癫痫发作率^[49-50]。但新技术也面临一些新的挑战,如植入设备续航时间短、治疗费用高

等。未来需优化治疗方式,进一步优化植入设备续航及医保覆盖策略^[51]。

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