

特发性震颤神经调控治疗进展

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【摘要】 特发性震颤是临床常见的运动障碍疾病,对于部分震颤症状严重、日常生活活动受到影响且药物疗效欠佳的患者可予以神经调控治疗,其疗效优于药物治疗。本文拟对特发性震颤的神经调控治疗最新进展进行综述,包括磁共振引导下聚焦超声、方向性电极和可感知脑深部电刺激术以及脑深部电刺激术最佳刺激靶点的临床研究,以为特发性震颤的治疗提供参考。

【关键词】 特发性震颤; 磁共振成像; 超声疗法; 深部脑刺激法; 综述

Progress on neuromodulation for treatment of essential tremor

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【Abstract】 Essential tremor (ET) is the most common movement disorder in clinical practice. Some patients' daily activities are affected because of the serious tremor. The current drug treatment for this disease is not effective, but the neuromodulation technique such as deep brain stimulation (DBS) is effective. This article provides a review of the latest developments in neuromodulation for the treatment of ET, including clinical trails on magnetic resonance-guided focused ultrasound (MRgFUS), directional-DBS and percept-DBS, as well as the optimal stimulation targets for DBS, in order to provide a reference for the treatment of ET.

【Key words】 Essential tremor; Magnetic resonance imaging; Ultrasonic therapy; Deep brain stimulation; Review

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特发性震颤(ET)是临床常见的运动障碍疾病,以运动时身体某部位的不自主、节律性、振荡性运动为特征性表现,病程进展缓慢,患病率为0.90%~5%,各年龄段均可发病^[1-3];不仅影响患者生活质量

和日常生活活动,严重者可致残^[4]。关于特发性震颤的病理生理学机制尚不完全清楚,但越来越多的神经影像学 and 尸检证据表明,小脑病变与其发病密切相关,尤其是小脑-丘脑-皮质回路在震颤的发生发展中发挥主要作用^[5-6]。目前临床常用的治疗药物包括抗癫痫发作药物(扑米酮、加巴喷丁、托吡酯)、抗惊厥药(苯二氮草类药物)和 β 受体阻断药(普萘洛尔),其中扑米酮和普萘洛尔为常用一线药物,但近50%患者疗效欠佳^[7-8]。神经调控技术是一种通过电、声、光、磁刺激技术对特发性震颤患者脑内失衡的运动传导通路进行调节以达到缓解症状的外科治疗方法,对于症状明显、严重影响生活质量且药物治疗无效的患者,无疑是较好的替代性选

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择。本文拟对神经调控技术治疗特发性震颤的临床研究进展进行概述,以为其治疗选择提供参考。

一、微侵袭性脑深部核团毁损术

立体定向脑深部核团毁损手术治疗特发性震颤已存在数十年,可有效改善震颤。1991年脑深部电刺激术(DBS)问世,其所具备的可逆性、双侧治疗安全性及神经刺激的可调节性等优点^[9-10],使得神经核团毁损手术在很大程度上不再是特发性震颤的主要治疗方法。然而,近年来微侵袭性脑深部核团毁损手术通过非侵入性技术如无需头皮切口、无需颅骨钻孔、无需无菌手术环境、无需麻醉、可日间手术等,重新引起关注。磁共振引导下聚焦超声(MRgFUS)亦称为“磁波刀”,是非侵入性神经核团毁损手术的最新技术,2013年首次用于治疗特发性震颤,并分别于2016和2018年获得美国食品与药品管理局(FDA)批准用于难治性特发性震颤和以震颤为主的帕金森病患者单侧丘脑核团毁损手术^[11]。手术时患者头部固定于立体定向框架,柔性硅胶膜密封头部与传感器之间空间,硅胶袋内填充冷却水(15~20℃)避免头皮过热^[12];根据术前结构性T₁WI确定的毁损靶点,采用低功率超声波聚焦三维角度调整靶点与超声波聚焦点的位置,确认二者重合后,通过聚集的高功率超声波穿过颅骨毁损相关神经核团(温度<60℃),使神经元发生凝固性坏死,治疗温度一般控制在40~49℃,术中实时评估震颤改善程度和不良反应^[13]。治疗过程中出现的短暂性不良反应包括头痛、头晕、恶心、呕吐、头皮温热感或感觉异常,但大多可于术后数小时内消失;当丘脑毁损范围略大或者毁损位置邻近丘脑腹尾核(VC)或锥体束时患者可出现感觉性麻木、步态障碍或肢体无力等症状且持续时间较长,通常需3个月方可消退。MRgFUS毁损术的准确度呈亚毫米级,照射后震颤症状即刻消失并迅速恢复正常活动且疗效具有长期性,患者术中始终保持清醒状态,可以实时反馈神经活动,便于术者进行术中评估^[14]。

1. 单侧丘脑腹中间核 MRgFUS 毁损术 Elias 等^[11]于2013年组织开展一项关于丘脑腹中间核(Vim)MRgFUS毁损术的随机双盲假对照临床试验,所纳入的76例特发性震颤患者中56例接受单侧Vim-MRgFUS毁损术,观察指标包括术后近期和远期手部震颤改善程度和不良事件发生率,结果显示,术后3个月时MRgFUS组震颤评分显著减少,由基线的18.10分降至9.60分,与20例假手术组患者

(16分降至15.80分)相比,组间差异为8.30分(95%CI:5.900~10.700, $P<0.001$),次要结局指标残疾和生活质量也有所改善(均 $P<0.001$),主要不良事件包括感觉异常和麻木[37.50%(21/56)]、步态障碍[35.71%(20/56)];术后12个月时,与基线相比,MRgFUS组震颤评分改善率提高至40%[(18.10±4.80)分对(10.90±4.50)分,95%CI:6.100~8.300],感觉异常和麻木下降至14.29%(8/56)、步态障碍降至8.92%(5/56),其中有19.64%(11/56)患者经历持续性神经系统不良事件。上述研究结果不仅表明MRgFUS毁损术治疗特发性震颤安全、有效,而且推动该技术获得2016年美国食品与药品管理局的批准^[11]。长期随访结果进一步证实,MRgFUS毁损术可使震颤患者(67例)术后2年震颤改善仍获益[震颤评分平均改善56%,(8.08±5.00)分],对残疾评分的改善可从基线(16.40±4.50)分持续至术后1年(5.40±5.30)分和2年(6.50±5.00)分,但感觉异常和步态障碍术后1年仍然存在(10例),少数(5例)患者甚至发生神经系统不良事件^[15];随访至第3年时,MRgFUS组无一例神经系统不良事件恶化,其中2例不良事件消失,无新发并发症^[16]。其他非盲法试验和Meta分析结果与Elias等^[11]的随机双盲假对照研究或开放标签扩展研究结果相似,术后3~6个月时,震颤评分改善率为40%~80%,短期不良事件发生率相似^[17-18];短期回顾性研究显示,MRgFUS毁损术相关严重不良事件发生率仅为1.60%^[19]。术后1年获益率与既往报道相似,但安全性更高且无严重不良事件,术后早期感觉异常和步态障碍发生率分别为17.14%(6/35)和2.86%(8/35),约77.14%(27/35)不良事件于术后第1个月消失;术后6个月不良事件发生率仅为2.86%(1/35),且所有不良事件均于术后1年消失^[20]。一项随访时间长达5年的开放标签研究发现,44例特发性震颤患者术后早期上肢震颤评分改善率为85%,但约11.36%(5/44)患者随访过程中震颤症状消失后又重新出现,并影响日常生活活动;大多数神经系统不良事件如共济失调等症状于术后3个月消失,但仍有11.36%(5/44)患者持续存在不良事件^[21]。

2. 双侧丘脑腹中间核 MRgFUS 毁损术 随着单侧Vim-MRgFUS毁损术治疗特发性震颤研究的广泛开展,2022年,美国食品与药品管理局及欧洲CE(Conformité Européene)认证批准双侧Vim-MRgFUS毁损术用于临床。多项前瞻性临床研究结果显示,

接受分期双侧 Vim-MRgFUS 毁损术治疗的患者,每次手术后震颤症状均可获得显著改善且无偏瘫、失语等严重功能障碍发生^[22-24];术后并发症或不良事件主要为短暂性肢体共济失调、头晕等^[24],或第 2 次手术后轻微或短暂性步态不稳(5/9)、原有步态不稳恶化(1/9)、构音障碍(1/9)或轻度口周麻木和感觉障碍(2/9)^[23],以及短暂性肩痛(2/11)、头痛(2/11)或恶心(1/11)等^[24],上述不良事件中的轻微或短暂性并发症一般术后 2~4 周或 3 个月即可完全缓解,但吞咽困难(2/10)可持续存在^[23],至于术后持续存在的口周或手指麻木、感觉异常(4/11)等,对患者日常生活活动并无明显影响^[24]。与单侧 Vim-MRgFUS 毁损术相比,双侧 Vim-MRgFUS 毁损术的疗效更佳,尤其是第 2 次手术后患者生活质量评分改善更为显著^[22,25]。大量临床实践证实,最初接受治疗的单侧肢体可持续受益于第 1 次手术带来的治疗效果,且第 2 次对侧治疗亦不会诱发严重或持续性不良反应;首次治疗后的随访观察既可了解相应震颤症状改善程度和不良反应发生情况,又可通过对毁损灶范围和疗效进行评估,为对侧手术“利弊得失”提供借鉴、有所提高,由此可见,分期单侧手术较同期双侧手术更为安全、患者获益更大。

由于微侵袭性脑深部核团毁损术的微侵袭性和不影响患者日常生活活动的优点,使其在第 2 次手术后具有较高的满意度,减少震颤、保护神经功能和认知功能是其治疗主要目标。既往针对单侧特发性震颤患者临床疗效的研究业已证实其疗效可靠、安全性良好^[26]。评估单侧 Vim-MRgFUS 毁损术的认知功能数据,对于规划双侧手术具有重要作用。从长期随访观察结果看,MRgFUS 毁损术对患者整体认知功能并无明显不良影响,甚至会使其有所改善,这可能是由于治疗后震颤所致注意力不集中、社会尴尬或焦虑情绪得以缓解,从而促进认知功能的提高^[27]。微侵袭性脑深部核团毁损术最常见的不良反应是构音障碍、共济失调和步态障碍。随着纤维束成像技术的临床应用,使得显示丘脑腹中间核区域内部解剖结构成为可能,进而提高靶点定位的精确度^[28-29],而且通过这项影像学技术可以准确判断 MRgFUS 毁损术后出现的症状是疾病相关症状还是毁损引起的新发症状,对降低不良反应发生率和严重程度大有裨益。MRgFUS 毁损术主要适用于高龄、伴其他合并症以及脑深部电刺激术或全身麻醉禁忌证的患者;不宜行 MRI 或颅骨较厚患者

为 MRgFUS 毁损术禁忌证^[30]。有研究显示,单侧 Vim-MRgFUS 毁损术与单侧 Vim-DBS 的疗效相近,后者可使轴向震颤患者获益更大,但 MRgFUS 毁损术改善生活质量的疗效更优($P < 0.001$);二者不良反应发生率存在显著差异($P < 0.001$),单侧 MRgFUS 毁损术后不良反应以步态障碍和(或)肌力降低为主($P = 0.003$),且持续时间更长($P = 0.038$),而单侧脑深部电刺激术则以局部不良反应如头痛、皮肤溃烂或电极部位疼痛更为常见($P < 0.001$)^[31]。因此认为,MRgFUS 是一种神经核团毁损方法,术后补救措施难以改善不良事件^[32]。单侧 MRgFUS 毁损术与单侧脑深部电刺激术的成本-效益比研究表明,前者成本更低(19779 英镑对 62348 英镑)且 5 年内每例患者可额外获得 0.03 个质量调整生命年(QALY, 3.71 年对 3.68 年),提示单侧 MRgFUS 毁损术除疗效和安全性外,尚具有成本效益的优势^[33]。

二、脑深部电刺激术

目前,脑深部电刺激术是难治性震颤的首选手术治疗方法^[34],丘脑腹中间核为其经典刺激靶点。与传统丘脑腹中间核毁损术相比,Vim-DBS 的疗效更佳、不良事件发生率更低^[9]。Vim-DBS 后严重不良事件主要包括颅内出血和软组织感染,但发生率较低^[35];常见不良事件程度较轻微如构音障碍、共济失调、感觉异常,单侧(20%~50%)和双侧(60%~85%)手术患者均可见,多与刺激强度有关,可通过调整刺激参数缓解症状,但部分不良事件是震颤获益的代价^[35]。一般而言,单侧 Vim-DBS 总体震颤改善率为 50%~60%而对侧上肢震颤改善率则高达 70%~90%^[35],即使术后 10 年,患者仍持续获益^[36]。然而,也有相关研究提示,随时间推移可有 10%~40% 患者震颤症状恶化,甚至术后 6 年平均恶化率 > 50%^[35]。由此可见,随着时间推移,通过逐步提高刺激强度控制震颤症状的方法可能增加“治疗窗”宽。这种因治疗获益程度下降而非疾病进展所出现的症状恶化现象称为“习惯化”或“适应化(habituation)”。为应对“治疗窗”范围受限导致的不良反应和习惯化震颤症状恶化等情况,近年推出方向性电极和可感知刺激技术,从而极大地提高脑深部电刺激术的治疗效果^[37-38]。

1. 方向性电极 当普通电极未直接植入目标靶点时,需要更多的电流以达到预定目标,如此将导致更大范围的靶点外组织被激活并诱发不良反应。而方向性电极的定向刺激则是在轴向平面上分割

脑深部电刺激术的电极触点,并对不同触点单独进行电流控制,使得轴向平面上的电流刺激方向可更精确地定位受益组织结构并避开易引起不良反应的结构。2020年,首次开展全球方向性电极与全向电极的前瞻性随机双盲对照临床试验,结果显示,与非定向刺激相比,10例接受定向刺激的特发性震颤患者“治疗窗”宽增加($P < 0.05$),其结果证实经较低的刺激幅度、较大的刺激电压(电流)不仅明显改善震颤症状且可使不良反应发生率降低^[37-38]。Dembek等^[39]于2016年首次对脑深部电刺激术电极位置和有效激活组织容积与震颤改善间的关系进行分析,展示概率刺激图(PSM)用于靶点选择和评估的有效性,提供有关特定区域预期脑深部电刺激术效应的先验信息,有助于临床医师后续对脑深部电刺激设备动态调整刺激参数。基于特发性震颤神经纤维局部和整体网络投射背景,引入刺激体积模型即脑深部电刺激术有效激活组织容积及组级分析表明,疗效显著提高^[40];通过方向性电极可以控制有效激活组织容积、增加“治疗窗”宽,进而改善震颤并降低不良反应发生率。目前临床常用的方向性电极主要来自美国 Medtronic、Abbott Laboratories 和 Boston Scientific 公司以及北京品驰医疗设备股份有限公司。

2. 可感知刺激技术 可感知刺激技术是一项通过脑深部电极检测和记录局部场电位(LFP)的技术。局部场电位是电极周围神经元整体电活动的矢量总和,与单个神经元的微电极记录不同,脑深部宏电极可记录更广泛的局部场电位和网络电活动信息。对特发性震颤患者局部场电位功率谱的研究表明,某些频段的神经元周期性振荡电活动与震颤频率及产生震颤的运动如意向性动作或姿势维持有关。第一代可感知功能设备于2016-2020年在美国和德国进行试用,复现了上述生物学标志物特征研究中的关键结果^[41]。基于上述初步研究,美国食品与药品管理局于2020年批准美国 Medtronic 公司生产的 Percept PC(植入式可感知脉冲刺激发生器)应用于临床,该设备可以记录不同电极触点之间的局部场电位,标志着可感知刺激技术开始在临床应用^[42]。自适应脑深部电刺激术(a-DBS)和闭环脑深部电刺激术(cl-DBS)是可感知刺激技术的应用,两个概念相互重叠,因此应用过程中可以互换。a-DBS并不以固定参数持续传递刺激,而是根据特定的输入信号反馈调整刺激;在特发性震颤的病理

性电活动下,输入信号既可是震颤频率,亦可是其所产生的生物学标志物。cl-DBS的刺激方式与传统脑深部电刺激术一样,均通过调节刺激电压、频率和脉宽进行刺激。理论上,a-DBS和cl-DBS均可根据对生物学标志物如特定节律局部场电位的识别,自动编辑日常刺激参数,以改善“治疗窗”宽、延长治疗获益时间和减少刺激能量消耗。2021年,He等^[43]首次对特发性震颤患者进行单纯基于丘脑局部场电位实时解码运动和震颤而触发的cl-DBS研究,自主运动、姿势以及任何相关震颤均可被检测到,灵敏度约为80%。基于局部场电位生物学标志物感知的小样本临床研究显示,a-DBS和cl-DBS对震颤生物学标志物的感知准确,可行性和有效性良好^[43-44]。对特发性震颤患者术后3、12和24个月丘脑腹中间核局部场电位的记录可以发现,诱发震颤的运动期间 β -LFP振幅显著降低,且其降低程度随时间的推移而变化(升高或降低),这种生物学标志物可长期用于闭环治疗^[44];Vim-DBS(cl-DBS)闭环刺激后6个月患者仍获益,且其疗效与开环刺激相当^[42];a-DBS后丘脑腹中间核 γ -LFP和皮质 β -LFP振幅降低,与传统脑深部电刺激术持续性刺激相比,治疗有效率约33.2%^[45];且Vim-DBS后姿势性震颤(4~7 Hz)相关 θ -LFP活动受抑制,随着震颤相关 θ -LFP、 α -LFP和 β -LFP振幅降低,震颤随之改善^[46],进一步印证这些病理性振荡活动参与震颤的病理生理学机制。

3. 最佳刺激靶点 随着Vim-DBS治疗特发性震颤的广泛应用,越来越多的靶点定位研究表明,刺激腹侧触点较背侧触点更有效,尤以刺激联合平面向下方触点效果更佳^[47],这些触点均位于丘脑底核后部(PSA)或尾侧未定带(cZI)附近。Barbe等^[48]于2018年即通过前瞻性、双盲、交叉验证研究对丘脑底核后部和丘脑腹中间核的靶点进行筛选,共纳入14例特发性震颤患者,13例完成电极植入手术,所用电极导线可同时穿过丘脑腹中间核和丘脑底核后部区域,导线背侧触点、中间触点和腹侧触点分别位于丘脑腹中间核、连合间线和丘脑底核后部,术后前3个月仅选择中间触点进行单极刺激,之后随机分配至丘脑腹中间核或丘脑底核后部触点,每一触点亦行单极刺激,为期2个月,随访期间(12个月),患者和医师可以根据临床判断动态调整刺激参数;至随访结束时,大多数患者(9/14例)选择刺激丘脑底核后部,仅少数患者(3/14例)以刺激丘脑腹

表 1 特发性震颤脑深部电刺激术刺激靶点相关研究

Table 1. The study of DBS stimulation targets in ET

文献来源	研究对象	刺激靶点(刺激时间)	不良反应	疗效	随访	结论
Sun 等 ^[59] (2024)	9 例患者先后随机接受双侧 Vim-DBS 和 PSA-DBS	Vim(4~7 个月)+PSA(8~11 个月) 或 PSA(4~7 个月)+Vim(8~11 个月)	PSA-DBS 更少发生言语和步态障碍	获得同等程度震颤抑制时,PSA-DBS 较 Vim-DBS 所需刺激强度更低	未报道	两个刺激靶点抑制震颤效果相当,但 PSA-DBS 改善疾病特异性生活质量更优
Fan 等 ^[60] (2022)	448 例患者分别接受双侧 Vim-DBS 和 PSA-DBS	326 例 Vim(未报道), 122 例 PSA(未报道)	Vim-DBS 不良反应发生率更高,两组构音障碍和共济失调发生率无差异	PSA-DBS 和 Vim-DBS 抑制震颤均有效	随访 12~24 个月内,PSA-DBS 较 Vim-DBS 更有效、安全	PSA-DBS 更有效、安全
Kvernmo 等 ^[49] (2022)	45 例患者先后随机接受双侧 Vim-DBS 和 PSA-DBS	Vim(0~3 个月)+PSA(4~6 个月) 或 PSA(0~3 个月)+Vim(4~6 个月)	两组不良反应发生率无差异	PSA-DBS 减轻震颤严重程度和震颤相关手部功能障碍更明显	随访 12 个月时,PSA-DBS 较 Vim-DBS 震颤改善更明显	PSA-DBS 改善手部震颤优于 Vim-DBS

Vim, ventral intermediate nucleus, 丘脑腹中间核; PSA, posterior subthalamic area, 丘脑底核后部; DBS, deep brain stimulation, 脑深部电刺激术

中间核为主,两个刺激靶点对震颤抑制率无明显差异(95%CI:-15.000~1.200, $P=0.086$),但刺激丘脑底核后部呈现震颤改善效果更好的趋势,两个刺激靶点单极刺激所诱发的不良反应相似,PSA-DBS 抑制震颤所需的电流更小。目前,大多数映射概率研究[又称组织有效刺激图谱研究(Probabilistic Mapping Studies)]及 2022 年 *Ann Neurol* 发表的 3 项研究^[49-51]均支持丘脑底核后部是控制震颤的最佳靶点。丘脑底核后部区域位于腹外侧丘脑下方、黑质上方、红核外侧、内囊内侧、丘脑底核后内侧及内侧丘系前方,亦包括来自小脑丘脑束(CTT)和中脑网状结构的传入纤维。2022 年来自 *Ann Neurol* 的社论指出,根据神经影像学技术提供的研究结果支持丘脑底核后部为抑制震颤的最佳靶点^[52]。晚近研究所绘制的 600 个刺激触点的有效激活组织容积业已确认,最佳刺激触点位于丘脑底核后部,同时包含丘脑腹中间核下缘组织^[49-51,53-54]。这些映射概率研究提供的数据提示,丘脑底核后部可以作为控制震颤症状的最佳靶点。上述研究中,Nowacki 等^[51]于 2022 年报告的回顾性分析结果是迄今样本量最大的研究,共计纳入 119 例特发性震颤患者,刺激触点激活区覆盖运动丘脑的大部分区域以及丘脑底核后部,最佳震颤控制的峰值强度区域从丘脑底核后部延伸至丘脑腹中间核中部,次优控制区域为丘脑底核后部前内侧至丘脑腹外核(Vop)。虽然各项研究中最佳触点位置略有不同,但仍可看出大多数触点位置均沿小脑丘脑束走行,与连接运动皮质、脑桥核、小脑、丘脑、再回到运动皮质的振荡活动的病理性通路有关^[55]。近期一项基于 DWI 序列的临床

研究结果显示,特发性震颤患者经 Vim-DBS 后运动丘脑与初级运动皮质(M1)纤维连接,并投射至小脑上脚^[56];且震颤症状的改善效果和触点与小脑丘脑束间的距离有关^[57],随后的概率纤维束成像技术亦进一步证实靶刺激的最佳触点邻近小脑丘脑束,丘脑底核后部触点通常比丘脑腹中间核触点更接近小脑丘脑束^[58]。近年发表的有关刺激靶点的研究参见表 1^[49,59-60]。

4. 新型刺激模式 传统脑深部电刺激术治疗特发性震颤主要采用持续、高频、阴极脉冲刺激模式。随着脑深部电刺激设备和技术的不断进步,为增加“治疗窗”宽、降低不良反应、提高疗效,在原有刺激模式的基础上,近年开发并在临床推广应用的新型刺激模式有对称性双相脉冲、阳极脉冲、短脉冲、低频刺激和恒流刺激等。一项随机双盲交叉设计试验对 9 例特发性震颤患者的分析显示,阳极脉冲治疗产生不良反应的刺激强度阈值[(3.27±1.42) mA 对 (2.14±1.10) mA, $P=0.008$]和不良反应阈值[(7.25±1.37) mA 对 (4.79±1.55) mA, $P=0.008$]显著高于阴极脉冲,且不良反应阈值提高幅度更大,因此阳极脉冲“治疗窗”宽(不良反应阈值与治疗阈值之差)显著高于阴极脉冲[(3.98±1.49) mA 对 (2.65±1.33) mA, $P=0.008$]^[61]。该项研究还发现,先阴极双相脉冲($P=0.047$)和先阳极双相脉冲($P=0.008$)的“治疗窗”宽较阴极脉冲显著延长^[61];同类研究亦证实先阳极双相脉冲的共济失调发生率明显低于传统阴极脉冲^[62],若于双相脉冲之间增加相间间隙尚可减少“治疗窗”宽^[63]。对短脉冲刺激疗效及不良反应的观察显示,与传统刺激(60 μs)相

比,短脉冲刺激(30 μ s)具有相同或更好的震颤抑制效果,且较少诱发共济失调和感觉异常^[64-65]。传统脑深部电刺激术采用恒压输送方法,但因导线与周围脑组织间阻抗的变化,输送的电流亦随时间推移而变化^[66],而采用恒流刺激,术后特发性震颤评分平均改善71%、特发性震颤日常生活活动能力总评分平均改善65%,提示恒流刺激可为特发性震颤患者提供有效的震颤抑制效果^[67]。

三、非侵入性神经调控技术

外周刺激治疗特发性震颤的主要技术是功能性电刺激(FES)和传入通路刺激^[68]。功能性电刺激是在运动阈值以上刺激周围神经或肌肉,从而使肌肉收缩以对抗震颤;传入通路刺激则是在运动阈值以下进行刺激,以改变传入信号并调节中枢震颤网络。与功能性电刺激的运动阈值以上刺激模式相比,传入通路刺激在实际应用中效果更佳,并具有更好的耐受性。目前,唯一通过美国食品与药品管理局批准的外周刺激方法是经皮传入模式刺激(TAPS),通过手环样腕部设备(美国Cala Health公司)交替刺激正中神经和桡神经,改变震颤节律以抑制震颤症状。该设备的有效证据来自两项随机假对照研究和一项开放标签研究,结果显示,>50%患者震颤改善率>50%,主要不良事件为手腕不适、皮肤刺激等^[18.87%(47/263)]^[69-70];中位持续获益时间为60 min^[70-71],刺激停止后获益时间短是该疗法的主要局限性。目前国内已有注册的特发性震颤外周刺激临床试验。经颅刺激共有3种技术,即重复经颅磁刺激(rTMS)、经颅直流电刺激(tDCS)和经颅交流电刺激(tACS)。重复经颅磁刺激是利用颅外磁场脉冲,而经颅直流电刺激和经颅交流电刺激则是通过对颅外电流的调控发挥作用,三者均可达到调控神经元激活阈值的目的^[72]。在当前技术限制范围内,非侵入性神经调控技术仅针对更广泛和更浅表的大脑区域;而针对小脑和辅助运动区施行的低频重复经颅磁刺激对震颤症状仅呈现轻微的抑制作用或无改善,但不良事件极少^[73]。目前尚无经颅刺激治疗特发性震颤的有效获益证据。

综上所述,特发性震颤发病率和病残率较高,晚近神经调控技术进展和未来发展方向在疾病治疗方面已展示出良好前景。过去5年中脑深部电刺激定向刺激技术和可感知刺激技术不仅拓宽刺激“治疗窗”和刺激效果,亦降低刺激所诱发不良事件发生率。丘脑底核后部可能是脑深部电刺激术治

疗特发性震颤的最佳靶点,新型刺激模式尚在探索中。丘脑核团MRgFUS毁损术在临床的应用是治疗特发性震颤的又一进展,该项技术提供了一种非侵入性治疗方式,具有较低的手术风险。特发性震颤的外周刺激装置也将在国内进入临床应用。未来,将对上述新技术的长期作用开展临床研究,以确定所观察到的短期疗效能否维持;同时,还应进一步完善刺激靶点的选择,希望基于病理网络的高级成像技术实现对特定解剖结构的靶点定位;探索针对特发性震颤更具个性化的神经调控方案,以期震颤抑制效果达到最大的同时,产生最少的不良事件。

利益冲突 无

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· 小词典 ·

中英文对照名词词汇(三)

- 化疗诱发的周围神经病变
chemotherapy-induced peripheral neuropathy(CIPN)
- 昏迷恢复量表-修订版
Coma Recovery Scale-Revised(CRS-R)
- 机器学习 machine learning(ML)
- 肌电图 electromyography(EMG)
- Burke-Fahn-Marsden肌张力障碍量表
Burke-Fahn-Marsden Dystonia Rating Scale(BFMDRS)
- Meynert基底核 nucleus basalis of Meynert(NBM)
- 激光间质热疗法 laser interstitial thermotherapy(LITT)
- 吉兰-巴雷综合征 Guillain-Barré syndrome(GBS)
- 脊髓电刺激术 spinal cord stimulation(SCS)
- 脊髓小脑性共济失调 spinocerebellar ataxia(SCA)
- 脊髓源性神经干细胞
spinal cord harbors neural stem cells(SC-NSCs)
- N-甲基-D-天冬氨酸受体
N-methyl-D-aspartate receptor(NMDAR)
- 间质性膀胱炎/膀胱疼痛综合征
interstitial cystitis/bladder painful syndrome(IC/BPS)
- SF-36健康调查简表 36-item Short-Form(SF-36)
- 健康相关生活质量 health-related quality of life(HRQoL)
- 交流质量 quality of communication(QDC)
- 脚桥核 pedunclopontine nucleus(PPN)
- 近红外光谱 near infrared spectroscopy(NIRS)
- 经耳迷走神经电刺激
transcutaneous auricular vagus nerve stimulation(taVNS)
- 经颅超声刺激 transcranial ultrasound stimulation(TUS)
- 经颅磁刺激 transcranial magnetic stimulation(TMS)
- 经颅交流电刺激
transcranial alternating current stimulation(tACS)
- 经颅脉冲电刺激
transcranial pulsed current stimulation(tPCS)
- 经颅随机噪声刺激
transcranial random noise stimulation(tRNS)
- 经颅直流电刺激
transcranial direct current stimulation(tDCS)
- 经皮传入模式刺激
transcutaneous afferent patterned stimulation(TAPS)
- 经皮迷走神经刺激术
transcutaneous vagus nerve stimulation(tVNS)