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·专论与综述·

丘脑底核 - 深部脑刺激术术后淡漠的研究进展 *

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摘要：帕金森病(Parkinson's disease，PD)是一种由于中脑黑质以及其他核团结构的多巴胺能神经元变性所致的以进行性运动功能障碍为主要表现的疾病。近年来，双侧高频刺激的丘脑底核 - 深部脑刺激术（STN-DBS）治疗 PD 效果确切，疗效较好，但其出现了术后淡漠等类似副作用，严重影响了 PD 治疗效果和患者的生活质量，引起了临床医生的高度重视。本文对 STN-DBS 术后淡漠发病情况、表现及治疗进行综述，为临床诊治提供思路。

关键词：帕金森病；丘脑底核 - 深部脑刺激术；淡漠

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Advances in Research on the Apathy of the Subthalamic Nucleus - deep Brain Stimulation*

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ABSTRACT: Parkinson's disease is characterized by progressive motor dysfunction owing to degeneration of dopaminergic neurons in the substantia nigra and other nuclei. Recently, the bilateral high frequency stimulation of the subthalamic nucleus deep brain stimulation (STN-DBS) as the treatment of PD was famous with good curative effect. But postoperative apathy as its side-effect impact on the therapeutic effect and the quality of life of patients seriously, which drawn the attention of clinicians. In this article, we summarized the incidence, manifestation and treatment of postoperative apathy and tried to provide some ideas for clinicians.

Key words: Parkinson's disease; STN-DBS; apathy

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帕金森病(Parkinson's disease，PD)是由于中脑黑质以及其他核团结构的多巴胺能神经元变性所致的，以进行性运动功能障碍为主要表现的疾病[1]。帕金森病的非运动症状也有严重的致残性，同时使帕金森患者常伴有精神异常。PD 药物治疗包括左旋多巴、多巴胺激动剂等，在治疗早期对运动障碍症状改善理想，但长期应用可致药效下降、运动期 " 开 - 关现象 " 出现等[2]。近年来，为了更加有效治疗 PD，减少长期药物治疗引起的并发症，双侧高频刺激的丘脑底核 - 深部脑刺激术（STN-DBS）手术实施率逐年上涨[3]。尽管 STN-DBS 显著改善 PD 患者的运动症状，但术后淡漠、抑郁的病例近年来报道屡见不鲜[4]，逐渐引起临床医生的重视。

1 STN-DBS 术后淡漠的患病率

一项荟萃分析 [5] 显示，PD 患者 STN-DBS 术后淡漠约占 8.2%。术后长期随访研究发现，在术后的前几个月中患者频繁出现一过性淡漠；在术后随访 5 年中，小部分患者出现永久性淡漠、随执行功能障碍逐渐加重以及痴呆。Thobois 等人报道在观察 STN-DBS 术后 1 年的 PD 患者中，有 54%的患者出现淡漠，平均发病时间为 4.7 个月[6]。而 Funkiewiez 研究则声称，术后 1 年、3 年淡漠发病率为术前的两倍[7]。有研究证实[8]，与药物治疗相比，STN-DBS 术后两年内的淡漠发病率无显著增加，而术后继续应用抗帕金森药物可降低淡漠发病率。有趣的是，也有研究报道 DBS 术后一年内淡漠发病率可高达 50%，这可能与患者依从性差、未口服抗帕金森药物等有关[7]。研究证实，所有 PD 患者术后立即停用多巴胺受体激动剂、左旋多巴减至最小量，同时调整电刺激参数，半数患者术后一年内出现淡漠，其中 50%合并抑郁[9]。总的来说，因病例样本选取及淡漠的评价标准不同，术后药物治疗方案亦不同，导致相关文献中 STN-DBS 术后出现淡漠的发病率也不同，16.5-42%不等[10]。

2 STN-DBS 术后淡漠的发病机制

STN-DBS 引起淡漠原因目前尚不清楚。术后淡漠可能依

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据神经相关环路混合的不同而不同,一项增长的证据也表明分散的脑区网络参与淡漠的发展,包括额 - 副皮层和运动环路[11],导致其存在多种类型,包括情感 - 情绪型、认知型和自体活动型[12]。此外,由于丘脑底核尺寸小、解剖结构特殊,使得 STN-DBS 电极植入处很接近非运动区,容易导致电流扩散到周围的非运动区和其邻近结构,损害上述环路。同时边缘叶神经回路与丘脑底核有紧密的连接,因此电刺激也可引起情感淡漠、躁狂和抑郁等症状[13,14]。有专家学者认为,STN-DBS 术后淡漠的发病与抑郁密切相关。Funkiewies 等人观察了一组患者 STN-DBS 术后抑郁症状明显加重同时合并淡漠[7]。但也有人认为术后淡漠与与抑郁可能为两个不同的神经环路介导,之间并无相互联系[15]。

不得不提,STN-DBS 术后左旋多巴胺减量引起淡漠、抑郁的病例也多有报道[16]。STN-DBS 术后患者运动障碍症状改善的同时,多巴胺能药物减量常引起以淡漠为主的戒断综合征。当然,STN-DBS 术后 PD 晚期淡漠一般认为是 - 突触核蛋白在脑神经元中扩散引起的病情进展,而非 STN-DBS 手术造成[17]。

3 STN-DBS 术后淡漠的临床特点

淡漠是 STN-DBS 术后较常见的非运动症状,目前多被定义为一种痛苦情绪导致的动机缺乏或非意识水平降低,术后淡漠患者在进行目标定向的活动时常常表现出行为、情绪和认知缺陷[18,19]。其多与单纯淡漠临床表现类似,表现为一组行为情感异常症状包括:对事物的兴趣及行动力减弱,没精打采,感情冷淡等。术后淡漠可引起认知功能下降并严重影响 PD 预后,甚至可引起患者营养不良、久坐不动等,严重时出现深静脉血栓[20]。有研究声称,STN-DBS 提高了 14-68%PD 患者的生活行为能力,但术后淡漠及其他非运动症状的出现亦使部分 PD 患者生活能力减退[21]。

4 STN-DBS 术后淡漠的影像改变

解剖学和影像学研究证实,前额叶皮质 - 纹状体神经环路异常可导致淡漠[22]。淡漠常被认为是与前额叶皮质、尾状核、苍白球以及背侧丘脑内侧核损伤相关[23]。影像学资料表明,淡漠多与眶额叶皮质灰质、前扣带回皮层灰质、前额叶背外侧皮层灰质萎缩相关[24]。功能核磁可发现淡漠患者眶额叶皮质灰质、前扣带回皮层灰质的基础代谢率明显下降[25,26]。有趣的是,PET 发现 STN-DBS 术后淡漠患者与单纯淡漠患者类似,中脑 - 边缘叶神经环路中多巴胺能递质转运异常,而这些改变却未出现在不伴有淡漠的 PD 患者中[27]。应用同位素 11C 标记的雷氯必利作为显像剂的 PET 发现术后淡漠患者的前额叶皮质、扣带回、杏仁核以及纹状体等结构多巴胺能 D2、D3 受体表达增加,内源性突触多巴胺含量下降[28]。最新研究报道,应用 18F-FDG PET 检测发现 STN-DBS 术后淡漠的发生与术前患者右侧大脑半球纹状体腹侧的代谢下降具有反相关性[29]。

5 STN-DBS 术后淡漠的治疗

目前已知,胆碱酯酶抑制剂、多巴胺能药物以及抗抑郁药物的应用可以改善 STN-DBS 术后淡漠。在一个随机双盲的研究中报道,31 例严重的 STN-DBS 术后不伴有痴呆和抑郁的淡漠患者应用卡巴拉汀 6 个月后,临床症状明显改善[30]。另一项探索性研究中显示,37 例 PD 患者 STN-DBS 术后淡漠,应用多巴胺 D2、D3 受体激动剂吡贝地尔显著改善淡漠症状[31]。同时,大剂量应用抗抑郁药物 - 醋哌甲酯 3 个月可显著降低晚期 PD 患者 STN-DBS 术后淡漠发生率[32]。尽管如此,目前 STN-DBS 术后淡漠应用抗抑郁药物仍存在争议。一些个案报道声称,STN-DBS 术后淡漠患者存在对 5- 羟色胺再摄取抑制剂、肾上腺素再摄取抑制剂以及阿米替林等抗抑郁药物抵抗,而仅对多巴胺能治疗敏感[33]。研究报道,由于淡漠的发生与患者是否存在运动症状以及认知功能障碍、抑郁等有关[34,35],所以在积极使用多巴胺类等的药物治疗和康复治疗淡漠的同时,需要积极纠正患者各种运动症状和非运动症状,同时加强心理干预治疗[36]。包括:对患者进行心理评估,与患者及其家属沟通,找准其心理症结;掌握患者的负性情绪和行为,多给予鼓励;通过听轻音乐,调节呼吸,哭泣发泄,肌松训练等方式帮助患者舒缓负性情绪,放松身心等[37]。

6 小结与展望

STN-DBS 近年来已经部分代替了 PD 的药物治疗和毁损手术治疗,逐步成为目前国际公认的最先进、最安全有效的治疗方法[38-40]。STN-DBS 使 PD 患者出现新的临床表现,主要为额叶痴呆、淡漠、左旋多巴抵抗的运动障碍症状,而无震颤及肌强直。PET 及功能核磁可早期发现 STN-DBS 术后淡漠患者脑区相关核团的代谢改变,但目前缺乏相关的大规模临床试验证据而未在临床普及。STN-DBS 术后早期可逆性淡漠与多巴胺能药物减量关系密切,积极应用多巴胺能受体激动剂或结合精神支持治疗可取得良好效果[41,42]。而 STN-DBS 术后 PD 晚期淡漠则多与α- 突触核蛋白在神经元中播散、患者认知功能恶化相关,多提示预后不佳。在药物治疗的同时辅助康复治疗及心理干预常可取得较好疗效。随着医疗科技的高速发展和国民生活水平的改善,STN-DBS 术后淡漠逐渐走入大众视野并迅速引起关注。希望本文的总结能为术后淡漠的诊疗提供新的思路,为术后淡漠的科研提供新的视角。

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