

# 帕金森病自主神经功能障碍丘脑底核 脑深部电刺激术治疗进展

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**【摘要】** 自主神经功能障碍是帕金森病的常见非运动症状,发生率高,涉及多系统功能紊乱,临床表现多样,严重影响患者生活质量。自主神经功能障碍可能是帕金森病晚期的主要症状,也是患者病残的主要原因。丘脑底核脑深部电刺激术(STN-DBS)是帕金森病中晚期的有效治疗方法,对运动症状的改善作用已得到广泛认可,但对自主神经功能障碍的作用尚未完全阐明。本文综述STN-DBS对帕金森病自主神经功能障碍的治疗进展,提高临床对自主神经功能障碍症状的重视程度,并对术前评估、靶点选择、刺激参数设定、药物调整、术后疗效判定等得以综合考虑,制定个体化治疗方案。

**【关键词】** 帕金森病; 自主神经系统; 深部脑刺激术; 丘脑底核; 综述

## Research progress of subthalamic nucleus deep brain stimulation in treatment of autonomic nerve dysfunction in Parkinson's disease

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**【Abstract】** Autonomic nerve dysfunction is a common non-motor symptom of Parkinson's disease (PD). It has a high incidence and involves multiple organ system disorders with various manifestations, seriously affecting the quality of life. Autonomic nerve dysfunction can be a major symptom of advanced PD and a major cause of disability. Subthalamic nucleus deep brain stimulation (STN-DBS) is an effective treatment for advanced PD, and its improvement of motor symptoms in PD patients has been widely recognized. However, the effect of STN-DBS on the symptoms of autonomic nerve dysfunction in PD patients is still unclear. Here, the efficacy of STN-DBS on PD autonomic nerve dysfunction is briefly reviewed. Therefore, we should pay more attention to the symptoms of autonomic nerve dysfunction in PD patients, and conduct preoperative evaluation of DBS in PD patients, so as to comprehensively consider the postoperative efficacy, target selection, stimulus parameter setting, drug adjustment, develop an individualized treatment plan.

**【Key words】** Parkinson disease; Autonomic nervous system; Deep brain stimulation; Subthalamic nucleus; Review

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自主神经功能障碍是帕金森病(PD)的常见非

运动症状,严重影响患者生活质量,加重运动障碍,增加经济负担<sup>[1]</sup>。自主神经功能障碍涉及多系统如胃肠系统、心血管系统、泌尿生殖系统、体温调节系统等功能紊乱,表现为直立性低血压(OH)、便秘、多汗、性功能障碍、吞咽困难、流涎等。丘脑底核脑深部电刺激术(STN-DBS)是帕金森病中晚期的有效治疗方法,对运动症状的改善作用已得到广泛认可,但对自主神经功能障碍的作用较少报道,缺乏多中

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心大样本随机对照试验,其疗效尚存诸多争议。本文拟综述 STN-DBS 对帕金森病自主神经功能障碍的治疗进展,以期提高临床重视程度,进行术前评估、术后疗效判定时考虑到自主神经功能,制定个体化治疗方案。

### 一、帕金森病自主神经功能障碍发生机制

帕金森病自主神经功能障碍主要包括胃肠功能障碍、心血管调节障碍、泌尿生殖系统功能障碍、体温调节障碍等,其发生机制与自主神经元破坏和  $\alpha$ -突触核蛋白( $\alpha$ -Syn)聚集形成路易小体(LB)有关,其中,神经元破坏包括神经元丢失、神经纤维变性和突触丢失。自主神经控制中心包括大脑皮质、岛叶、下丘脑、脑干和脊髓,这些脑区均可发生神经元破坏和  $\alpha$ -Syn 聚集<sup>[2]</sup>;外周自主神经系统、迷走神经、交感神经等神经纤维以及支配消化系统、心脏、泌尿系统的神经丛也可出现神经元破坏, $\alpha$ -Syn 聚集亦常见,甚至早于自主神经元破坏<sup>[3]</sup>。此外有研究表明,帕金森病自主神经功能障碍还与遗传因素有关,基因变异致家族性帕金森病与自主神经功能障碍相关,例如, $\alpha$ -Syn 家族性突变 E46K 致家族性帕金森病患者病程早期即出现自主神经功能障碍,甚至发生于帕金森病前驱期<sup>[4]</sup>。环境因素如环境毒素、细菌和病毒感染等也可导致  $\alpha$ -Syn 聚集,引发自主神经功能障碍。

### 二、丘脑底核脑深部电刺激术对自主神经功能的作用机制

STN-DBS 对自主神经功能的作用机制取决于受刺激的解剖区域。基底节与调节自主神经功能的脑区相联系,进而影响自主神经功能<sup>[5]</sup>,但长期刺激丘脑底核是否影响自主神经功能尚不清楚。刺激丘脑底核可以出现泌汗、面部潮红、心率和血压升高<sup>[6]</sup>,其潜在机制尚不清楚,目前有两个假设理论包括间接激活边缘系统或间接刺激自主神经中枢网络,均可能发生于丘脑底核附近<sup>[7]</sup>。此外,STN-DBS 术后自主神经功能障碍的改善还可能与抗帕金森病药物剂量减少、运动功能改善有关<sup>[8]</sup>。

### 三、丘脑底核脑深部电刺激术对帕金森病自主神经功能障碍的疗效

1. 直立性低血压 直立性低血压系直立位血压下降并常伴有头晕<sup>[9]</sup>,主要表现为头晕、视力模糊、晕厥及其他较轻的症状如认知功能障碍、呼吸困难、颈肩部不适。此类患者直立位收缩压较平卧位下降  $\geq 30$  mm Hg 或者直立倾斜试验(HUTT)下降  $\geq$

30 mm Hg,和(或)舒张压下降  $> 15$  mm Hg<sup>[10]</sup>。直立性低血压在帕金森病患者中较为常见,其发生率可达 30%,并且随病程进展和疾病严重程度的加重而增加<sup>[9-11]</sup>,可以增加跌倒风险,影响日常生活活动能力<sup>[12]</sup>。左旋多巴和大多数抗帕金森病药物可不同程度加重直立性低血压<sup>[11]</sup>。STN-DBS 对帕金森病患者直立性低血压的短期效果存在差异。Herring 等<sup>[13]</sup>报告 6 例帕金森病伴直立性低血压患者,采用脑深部电刺激术刺激丘脑底核背侧部分靶点可以改善对血管压力感受器的敏感性,进而改善直立性低血压症状。LeWitt 等<sup>[14]</sup>对 14 例帕金森病伴直立性低血压患者行 STN-DBS,术后直立倾斜试验显示,STN-DBS 可提高外周血管收缩和压力反射的敏感性,从而有利于血压稳定。Tateno 等<sup>[15]</sup>发现,8 例行 STN-DBS 的帕金森病伴直立性低血压患者术后 6 个月时,体位性眩晕和晕厥发作次数明显减少,直立位收缩压自术前下降 51.60 mm Hg 减少至术后下降 17.30 mm Hg( $P < 0.05$ )。Heimrich 等<sup>[16]</sup>评估 24 例帕金森病患者心血管功能障碍,结果发现,STN-DBS 术后 6 个月直立性低血压发生率自术前的 45.8% 降至 12.5%。而 Bunjo 等<sup>[17]</sup>的研究并未显示出 STN-DBS 对帕金森病伴直立性低血压有改善作用。STN-DBS 对帕金森病患者直立性低血压的长期效果同样存在差异。一项纳入 11 例 STN-DBS 术后帕金森病患者(DBS 组)和 8 例最佳药物治疗帕金森病患者(药物组)的队列研究显示,随访 1 年时两组心率变异性(HRV)相似,但 DBS 组心血管功能障碍发生率高于药物组,表明减少药物治疗并不能阻止心血管功能障碍的进展<sup>[18]</sup>。一项研究对 36 例帕金森病进展期患者行 STN-DBS,术后 24 个月时包括直立性低血压在内的大部分非运动症状未发生明显变化<sup>[19]</sup>。Cani 等<sup>[20]</sup>对 20 例帕金森病患者 STN-DBS 术后 6 个月进行心血管反射试验(CRT)和直立倾斜试验评估,结果发现,STN-DBS 对直立性低血压无直接影响,STN-DBS 术后直立性低血压病例数减少可能是由于拟多巴胺药减少,因此认为,直立性低血压并非 STN-DBS 的禁忌证,实际上 STN-DBS 可以作为左旋多巴诱导直立性低血压的一种治疗选择。Benedetti 等<sup>[21]</sup>认为,帕金森病患者 STN-DBS 术后刺激特定的丘脑底核亚区可使心率发生不同程度变化,例如,刺激丘脑底核背侧和未定带可导致心率增快,且不受患者是否知晓开启刺激的影响;刺激丘脑底核腹侧和黑质网状部,只有患者知晓开启刺

激的情况下方可显著增快心率,可能是由于丘脑底核背侧和未定带直接参与自主神经的调控,而腹侧和黑质网状部可能参与丘脑底核联络区和边缘区相关的自主神经调控<sup>[22]</sup>。Aygün等<sup>[23]</sup>报告1例女性帕金森病患者STN-DBS术后发生晕厥,发现其右侧电极置于丘脑底核中心、左侧电极置于丘脑底核前部,术中以5 mA刺激左侧丘脑底核时,患者出现晕厥前症状,停止刺激后症状有所改善;术后早期以1.3 mA刺激右侧丘脑底核时,患者出现晕厥前症状并随后发生晕厥。Bunjo等<sup>[17]</sup>报告14例行STN-DBS的帕金森病患者,3例开启刺激时出现直立性低血压,2例关闭刺激时出现,3例开启和关闭刺激时均出现。上述研究证实STN-DBS术后进行自主神经症状筛查具有重要作用,即使是术前无自主神经症状的患者,主要包括心率变异性检测和直立倾斜试验<sup>[24]</sup>,用于评估两条对血流动力学有重要作用的自主神经输出途径——心脏交感和副交感神经系统的影响。由此可见,STN-DBS对帕金森病伴直立性低血压的短期和长期效果尚未形成一致性结论,未来有待更多的基础与临床研究尤其是随机对照试验进一步阐明STN-DBS对直立性低血压的作用机制并明确治疗效果。

2. 便秘 有20%~70%的帕金森病患者有便秘症状,且常出现于运动症状前<sup>[25-26]</sup>。多种因素可导致帕金森病患者便秘,且其发生率随疾病进展而升高<sup>[25]</sup>。其发生机制可能为 $\alpha$ -Syn在肠道系统中聚集并沿迷走神经扩散至脑神经,从而导致结肠蠕动功能减退<sup>[25]</sup>。目前关于STN-DBS对便秘改善作用的研究较少<sup>[27]</sup>。有两项研究分别对36和30例帕金森病患者双侧STN-DBS术后进行为期12~24个月的随访,均采用国际运动障碍协会统一帕金森病评价量表(MDS-UPDRS)评估非运动症状,发现STN-DBS可显著改善便秘<sup>[17,28]</sup>。另一纳入10例行STN-DBS的帕金森病患者的随访研究亦得出类似结论,采用罗马Ⅲ成人功能性胃肠疾病诊断调查问卷以及术后每日记录肠道日记,结果显示,术后6个月便秘症状显著改善<sup>[29]</sup>。推测是由于STN-DBS通过促进胃排空、增加胃肠蠕动,从而改善便秘<sup>[30]</sup>。一项针对17例帕金森病患者行双侧STN-DBS术后的随访研究采用帕金森病非运动症状量表(NMSS)评估便秘等非运动症状,结果显示,术后12个月便秘症状显著改善<sup>[31]</sup>。亦有研究得出不同的结果。一项针对56例行双侧STN-DBS的帕金森病患者进行至少1年

的随访研究结果显示,STN-DBS对便秘症状的改善效果欠佳<sup>[32]</sup>。一项长期随访研究共纳入26例帕金森病患者,STN-DBS术后随访1、5和11年,根据MDS-UPDRS评分,末次随访时5例出现新的便秘症状,2例存在严重便秘<sup>[33]</sup>。由此可见,STN-DBS对帕金森病患者的便秘症状短期内有改善作用,而随病程延长,其作用逐渐减退甚至加重便秘。

3. 排尿障碍 排尿障碍可见于38%~71%帕金森病患者,尤以夜尿最常见,其次是尿频、尿急<sup>[11]</sup>。即使是在疾病早期,有64%~87%的未经治疗的帕金森病患者可出现下尿路症状,其中约1/3症状较严重<sup>[34]</sup>。帕金森病排尿障碍与膀胱容量减少有关,并伴膀胱逼尿肌反射亢进和膀胱不自主收缩<sup>[35]</sup>。STN-DBS可直接作用于基底节多巴胺- $\gamma$ -氨基丁酸能直接通路和导水管周围灰质,在膀胱充盈过程中激活前扣带回皮质和前额皮质以抑制排尿,也可通过刺激大脑皮质控制膀胱张力<sup>[36-37]</sup>。一项多中心回顾性研究纳入57例行双侧STN-DBS的帕金森病患者,术后6个月采用帕金森病预后量表-自主神经功能部分(SCOPA-AUT)评估自主神经功能,结果显示,STN-DBS可以改善帕金森病患者自主神经功能障碍,尤以排尿和体温调节改善更明显<sup>[38]</sup>,究其原因,术后膀胱容量和反射量增加,进而有效控制排尿<sup>[39]</sup>。一项对16例帕金森病患者STN-DBS术后进行为期6~29个月随访的研究显示,开启刺激可使排尿反射正常化和膀胱容量改善,关闭刺激则发生反转,提示STN-DBS可改善排尿障碍<sup>[40]</sup>。一项Ⅳ期临床试验对6例帕金森病患者STN-DBS术后行国际前列腺症状评分(IPSS)和压力流量研究(PFS),结果显示,开启刺激IPSS评分、逼尿肌不自主收缩能力、膀胱容量均获显著改善,表明STN-DBS可以改善帕金森病患者排尿障碍<sup>[41]</sup>。一项回顾性研究对416例帕金森病患者STN-DBS术后采用美国泌尿协会症状指数(AUA-SI)、膀胱过度活动症评分(OABSS)和尿动力学检测等评估排尿功能和膀胱储存功能,发现STN-DBS可有效改善尿频、尿急和尿失禁等症状<sup>[42]</sup>。一项研究报道9例双侧STN-DBS术后膀胱充盈和排空情况,并采用PET观察局部脑血流量(rCBF)变化,发现开启刺激与丘脑后部和岛叶皮质rCBF变化显著相关,表明STN-DBS可促进排尿相关感觉控制<sup>[43]</sup>。一项针对早发型帕金森病患者的研究采用电话问卷调查STN-DBS的疗效,发现术后膀胱功能显著改善<sup>[44]</sup>。然而,一项针对14例帕

金森病患者STN-DBS术后7年随访的研究显示,随着病程进展,尿失禁症状亦持续进展<sup>[45]</sup>。

4. 吞咽障碍 吞咽障碍是帕金森病的常见非运动症状,发生率为11%~100%<sup>[46]</sup>,可以导致吸入性肺炎,是患者死亡的主要原因<sup>[47]</sup>。其发生机制可能与基底节回路、脑干吞咽中枢功能障碍、黑质变性相关,非多巴胺能脑区的路易小体及支配咽肌的外周运动和感觉神经的 $\alpha$ -Syn亦可导致吞咽障碍<sup>[48]</sup>。帕金森病患者 $\alpha$ -Syn在舌咽神经、迷走神经咽喉部感觉分支和喉上神经聚集,导致咽部感觉神经受累,咽部感觉减弱,引发吞咽障碍和误吸,主要表现为咀嚼困难、食物移动困难、食物在喉部堆积感,以及吞咽前、吞咽中或吞咽后哽咽或咳嗽,严重影响生活质量<sup>[48-49]</sup>。视频透视吞咽检查(VFSS)显示,STN-DBS对帕金森病患者的吞咽功能有改善作用,可能是由于STN-DBS调节神经回路,激活黑质纹状体多巴胺能通路、刺激丘脑底核投射至中脑被盖谷氨酸能神经元间接激活黑质纹状体多巴胺能神经元、直接刺激背侧前脑束,从而增强舌部和咽部运动<sup>[50]</sup>。一项研究对帕金森病患者行双侧STN-DBS,分别予以低频(60 Hz)和常规(130 Hz)电刺激,术后6周时VFSS检查显示,低频电刺激有助于吞咽功能的改善<sup>[51]</sup>。亦有研究显示,单侧STN-DBS可加重帕金森病患者吞咽障碍,究其原因,丘脑底核体积相对较小,电刺激易扩散至邻近区域,一旦刺激到皮质核束,可使受刺激区域功能恶化,导致吞咽障碍加重<sup>[52]</sup>。

5. 流涎 流涎常发生于帕金森病早期,其发生率为42%~55%<sup>[53]</sup>。目前尚不清楚其发生机制,可能与大脑皮质-边缘系统-纹状体-小脑和皮质-皮质网络的功能连接异常<sup>[54]</sup>,唾液分泌流速增加,或口面部肌张力障碍、吞咽困难等相关<sup>[55]</sup>。一项研究对61例帕金森病晚期患者行STN-DBS,对比分析手术前后自主神经症状,发现术后6个月流涎症状无明显改善<sup>[56]</sup>。亦有研究显示,STN-DBS对帕金森病患者的流涎症状具有轻微改善作用<sup>[57]</sup>。有研究采用帕金森病唾液分泌临床分级(SCS-PD)对22例伴流涎的帕金森病患者STN-DBS术后流涎程度进行评估,发现术后6个月流涎症状明显改善<sup>[55]</sup>。基于fMRI的STN-DBS改善帕金森病患者流涎症状的机制研究显示,STN-DBS术后双侧感觉运动皮质、顶上和顶下小叶及右侧枕叶与壳核的功能连接显著降低<sup>[58]</sup>。唾液分泌减少可能是由于STN-DBS调节

丘脑皮质或脑干相关区域,从而改善口面部僵硬、舌咽运动迟缓<sup>[22]</sup>。

#### 四、小结与展望

STN-DBS术后帕金森病患者部分自主神经功能障碍症状得以改善,亦有部分自主神经功能障碍症状保持不变甚至恶化,其确切机制尚未完全明确,有待进一步阐明脑深部电刺激术与自主神经功能障碍之间的关系,重点关注疾病进展、抗帕金森病药物及电极位置在其中的作用。此外,扩散张量成像(DTI)和白质纤维示踪成像(WMFT)不仅有助于更好地理解帕金森病神经回路,而且还增加特定白质纤维束作为脑深部电刺激术治疗靶点的可能性。自主神经功能障碍严重影响帕金森病患者的生活质量,临床医师应在术前评估主要运动症状的同时,关注自主神经功能障碍症状并进行综合评估,同时关注STN-DBS术后症状变化,结合运动症状的改善精准植入电极,予以个体化电刺激,确定最佳触点及其刺激参数并进行相应药物调整,以提供个体化医疗和护理管理。未来,脑深部电刺激硬件、编程、神经影像学和手术技术的进步,以及远程程控、自适应脑深部电刺激术、新的治疗靶点的应用可以使手术疗效和安全性逐步提高。

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