·专题综述·

帕金森病构音障碍

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【摘要】 构音障碍是帕金森病的常见运动症状，发病率较高，临床表现多样。帕金森病患者常忽视自身构音障碍，直至进展为失代偿阶段，仅少数患者接受相应治疗。本文综述帕金森病构音障碍发病机制、评估及治疗方法，以为帕金森病构音障碍的早期诊断和及时治疗提供理论依据。

【关键词】 帕金森病； 构音障碍； 综述

Dysarthria in Parkinson´s disease

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【Abstract】 Parkinson's disease (PD) is a common neurological degenerative disease in clinical practice. Dysarthria is a common motor symptom, with a high incidence and diverse clinical manifestations. PD patients often ignore their dysarthria symptoms until they reach the decompensation stage, and only a small number of patients receive treatment. This article reviews the pathogenesis, evaluation and treatment of dysarthria in PD, providing theoretical basis for early diagnosis and timely treatment of dysarthria in PD.

【Key words】 Parkinson disease; Articulation disorders; Review

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帕金森病是一种以震颤、肌强直和运动迟缓为主要症状的慢性神经系统变性疾病[1]，其特征性病理改变为多巴胺能神经元丢失、黑质致密部神经元色素脱失和路易小体(LB)形成。目前主要为药物治疗，包括拟多巴胺类药物、多巴胺受体激动药等，脑深部电刺激术(DBS)等手术治疗可以作为疾病晚期的补充治疗。构音障碍是帕金森病患者常见的运动症状，发生率约为89%[1]，且随疾病进展逐渐加重，导致生活质量下降[2]。目前仅有3%～4%的帕金森病构音障碍患者接受相应治疗[3]，有研究者将帕金森病构音障碍统称为低动力型构音障碍(HKD)[4]，主要表现为声音强度减弱、单一响度、单一音调、刺耳音质、发音迟缓、声音颤抖等特征[5]。构音障碍在特发性快速眼动睡眠期行为障碍(iRBD)和帕金森病早期阶段即已存在[6-7]，提示其可作为潜在的帕金森病早期甚至前驱期诊断标志物[5]。帕金森病患者通常忽视构音障碍症状，直至进展至失代偿阶段[8]；近年发现，构音障碍与帕金森病患者轻度认知障碍(MCI)相关[9]，姿势不稳型帕金森病患者构音障碍较静止性震颤型患者更严重，与步态障碍表型呈现出一致性趋势[10]，且构音障碍的加重可提示疾病进展[11-12]，因此，应重视帕金森病构音障碍的早期诊断与治疗[13]。本文拟综述帕金森病构音障碍的发病机制、评估及治疗方法，以为帕金森病构音障碍的早期诊断与及时治疗提供理论依据。

一、帕金森病构音障碍发病机制

构音功能是在中枢和周围神经系统调节下各种运动协调的结果，包括呼吸、发音、共鸣和产生韵律的过程，任意过程障碍均可导致构音障碍。帕金森病构音障碍发病机制尚未完全阐明，目前研究主要支持多巴胺能通路变性、非多巴胺能通路变性、

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听觉反馈障碍和神经网络激活[14]。

1.多巴胺能通路变性 进行性黑质纹状体多巴胺能通路变性是帕金森病构音障碍的原因之一[5]。男性帕金森病患者可观察到单一音调与尾状核多巴胺能神经元丢失相关,提示多巴胺能通路变性与帕金森病构音障碍存在关联性,但这一现象并未在女性患者中观察到[15]。由于拟多巴胺类药物对帕金森病构音障碍缺乏明显效果,提示多巴胺能通路变性在疾病发生发展中的作用尚无定论[16-17]。研究显示,长期应用左旋多巴可能导致帕金森病患者构音障碍加重、言语流畅性降低、口吃风险增加[18]。拟多巴胺类药物对帕金森病构音障碍的影响取决于多种因素的协调作用,包括帕金森病临床表型、药物"关"期构音障碍特征及对拟多巴胺类药物反应性[19],同时易受患者自身对构音障碍代偿性改善程度的影响[20]。

2.非多巴胺能通路变性 非多巴胺能通路变性被认为是帕金森病构音障碍进展的原因之一[21]。帕金森病患者疾病早期即可出现构音障碍,与脑干运动系统相关的非多巴胺能神经递质如胆碱能、谷氨酸能神经递质在疾病早期亦受损[22]。相比之下,多巴胺能神经递质耗竭通常发生于疾病相对较晚阶段。在其他非帕金森病疾病状态中,如化疗药物伊立替康与乙酰胆碱酯酶(AChE)结合使其失活引起结直肠癌患者孤立性短暂性构音障碍[23],提示胆碱能系统在构音障碍的发生发展中也发挥重要作用。随着疾病进展,帕金森病患者构音障碍逐渐加重,但与运动障碍严重程度并无相关性,且拟多巴胺类药物治疗效果欠佳[22],因此认为帕金森病构音障碍是多巴胺能和非多巴胺能通路变性共同作用的结果。

3.听觉反馈障碍 研究发现,帕金森病患者无法自发维持或改变自身声音强度,尽管帕金森病患者倾向保持较低的声音强度且抱怨提高音量后高于平常声音强度,当患者接收到明确外界提示时可以将声音强度增加至少5~10 dB声压级,并认为这种自发语音与收到外界提示后声音强度控制之间的差异是颞上回听觉反馈区域损伤所致[24-25]。帕金森病患者对音高和音量变化产生的听觉反馈幅度明显高于健康人群[26-27],其中听觉感知异常和感知处理异常是帕金森病患者听觉反馈障碍的重要表现[24,27-28],这些异常可出现于帕金森病患者尚未察觉构音改变之前[26]。

4.神经网络激活 语言功能是复杂神经网络协调产生的生理活动,其中涉及构音功能的脑区包括背侧语言通路的皮质及皮质下结构、基底节、丘脑和小脑[29-30]。帕金森病构音障碍与主要运动区如口面部运动皮质区、小脑、前运动区(PMA)和前额皮质等的募集改变有关[31-32];丘脑底核(STN)言语神经元功能减退可以导致帕金森病患者发音时间延长[33-34];纹状体和前额皮质之间相互作用也可能是帕金森病患者构音障碍的原因[35]。从脑结构改变角度,梭状回和右侧中央前回萎缩与帕金森病构音障碍存在一定关联性[36]。帕金森病患者主动发声时大脑皮质水平事件相关电位(ERP)P2振幅增高,且较被动聆听时P2振幅更高[28],提示主动发声时存在神经网络激活。

二、帕金森病构音障碍评估

1.主观评估 嗓音障碍指数(VHI)是一项经过神经心理学测验验证的主观知觉自评量表,目前广泛用于评估多种病理状态下构音障碍严重程度及药物治疗、行为疗法、手术治疗等的功能性治疗结果[37-39],主要从情绪、功能和躯体三方面(共30项条目)评估帕金森病构音障碍对患者造成的社会心理负担[40],其评估结果可靠、有效,已被翻译为多种语言版本广泛应用。

2.客观评估 Frenchay构音障碍评定表(FDA)是一种标准化、经广泛验证的神经系统疾病相关异常口腔运动评价量表[41],包括反射(咳嗽反射、吞咽反射、流涎反射)、呼吸、唇部、下颌、上颚、喉部、舌的活动及构音清晰度等28个维度,其有效性和可靠性已在不同国家和地区针对不同语言群体患者的多项研究中得到证实[42-43]。其他客观评估还包括声学指标如声音强度、发音持续时间、发音基频和元音发音,已用于构音障碍的评估。帕金森病构音障碍患者声音强度、发音持续时间、平均基频、最大基频、最小基频和发音稳定程度与健康人群存在显著差异,且构音障碍严重程度与发音结束时基频、发音持续时间和谐波噪声比(HNR)改变程度密切相关[44]。应注意的是,临床实践中可观察到主观评估与客观评估之间存在一定差异,推测可能是帕金森病患者对渐进式构音障碍良好适应的结果[45]。

三、帕金森病构音障碍治疗

1.药物治疗 抗帕金森病药物主要为改善多巴胺能通路退行性变的拟多巴胺类药物[46-47],可以改善运动症状,但其治疗帕金森病构音障碍的有效性

尚无定论。纵向研究表明，帕金森病患者予以拟多巴胺类药物后言语功能得以保留或有所改善[48]。左旋多巴对帕金森病患者言语功能的改善程度与言语障碍严重程度和独特言语表型有关[17,22,49]，不会给早期帕金森病患者带来明显的声学特征改变，至治疗后期其对言语功能的改善甚至可以忽略不计[16,19,50]；亦有研究显示，长期服用拟多巴胺类药物可能导致构音障碍[51]。单胺氧化酶B抑制剂可以防止多巴胺降解，但有研究表明，未经左旋多巴治疗的早发型帕金森病患者经单胺氧化酶B抑制剂治疗后构音障碍并无法改善[52]。

2.手术治疗 （1）苍白球腹后部切开术（PVP）：苍白球腹后部切开术是一种立体定向手术，可以缓解帕金森病运动症状和药物引起的运动障碍，而对帕金森病构音障碍的作用尚不明确。初步研究表明，帕金森病患者苍白球腹后部切开术后的声学指标有所改善，但易受患者自身因素的影响[51]。（2）脑深部电刺激术：脑深部电刺激术是一种对帕金森病震颤、肌强直和运动迟缓长期有效且安全的治疗方法[53]，其刺激参数通常针对运动症状进行优化，但对帕金森病构音障碍的作用尚不明确，刺激靶点主要为丘脑底核和苍白球内侧部（GPi），但STN-DBS和GPi-DBS可能对帕金森病构音障碍产生不同影响[54]。STN-DBS通过改善发音相关器官的运动功能减退、僵硬和震颤以改善声音强度、声音颤抖程度、言语清晰度和自然度[55]，已证实双侧STN-DBS可以促进帕金森病患者单词、短句生成并提高言语自然度[56]。将刺激器植入丘脑底核前部感觉运动区可以改善发音时呼吸道气流，从而改善帕金森病构音障碍[57]。亦有多项研究证据表明，脑深部电刺激术对帕金森病构音障碍无效，且有可能加速其进展[58-62]。与双侧STN-DBS相比，单侧STN-DBS导致严重构音障碍的风险较低[63]。过度刺激左侧丘脑底核可使帕金森病轴性症状恶化，包括构音障碍加重[64]，可能是由于过度刺激左侧丘脑底核导致信息处理速度减慢、锥体束激活[65-66]。STN-DBS刺激参数不同，治疗效果亦不同，自适应脑深部电刺激术（aDBS）可以预防传统连续脑深部电刺激所引起的构音障碍[67-68]；刺激频率不同，对构音障碍的影响亦不同，与高频刺激相比，低频刺激对轻度震颤及术后早期出现轴性症状患者的整体运动功能和轴性症状改善更明显[69-70]，且可部分逆转高频刺激引起的构音障碍[71-72]，但仍有研究者认为低频刺激无法改善帕金森病构音障碍[73]。脑深部电刺激术电极定位的细微变化亦对帕金森病患者运动和语言功能产生不同影响[56]，同时确定最佳的丘脑底核电极植入轨迹可减少构音障碍的发生[74]。不同言语障碍表型的帕金森病患者予以STN-DBS后构音障碍可能以不同的方式改善或恶化[75]：声音强度降低或声音震颤患者的构音障碍改善；而呼吸道气流受损患者的构音障碍加重，但语音清晰度与治疗前保持一致[76]。精心设计STN-DBS最佳治疗参数可以协调手术治疗带来的运动改善和构音改善[77]，证实精准手术参数的必要性。与之相比，GPi-DBS相关言语不良事件较少[78]，可能是由于苍白球内侧部作为刺激靶点其体积更大且主要由运动区组成，不易影响其他脑区功能[79]。亦有研究发现，GPi-DBS可对发音时共鸣、韵律和喉部功能产生负面影响，可能加重或诱发低动力型构音障碍、口吃、痉挛性构音障碍或共济失调性构音障碍[80]。（3）声带注射喉成形术（IAL）：部分帕金森病患者因声带闭合不全导致声门关闭不全[81]。声带注射喉成形术是临床应用广泛的声门关闭不全辅助治疗方法，通过临时声带注射填充或永久材料植入，可减轻因解剖结构改变而导致的帕金森病构音障碍[82]。（4）丘脑切开术：对于部分运动症状难以控制且不适宜行脑深部电刺激术的帕金森病患者，丘脑切开术是一种可行选择。亦有研究发现，丘脑切开术可以导致帕金森病患者出现不可逆性构音障碍。此外，无论手术部位位于优势半球还是非优势半球，单侧丘脑切开术均可以加重构音障碍，而双侧丘脑切开术则与单词阻塞（word blocking）、发音迟缓、低音调（hypophonia）等构音障碍持续恶化有关，这些明显的不良反应使丘脑切开术无法作为帕金森病构音障碍的治疗选择[52]。（5）聚焦超声消融手术（FUSA）：聚焦超声消融手术是一种对脑结构进行靶向损毁的无创性治疗方法，以苍白球内侧部为靶点可安全、有效改善帕金森病患者运动症状，但并尚未发现对帕金森病构音障碍有效，且可能引起较持久的构音障碍[83]；以丘脑底核为靶点也存在类似不良事件[84-85]，提示尚待探索平衡各种手术治疗方案以为帕金森病患者带来运动和构音改善。

3.非侵入性治疗 （1）重复经颅磁刺激（rTMS）：重复经颅磁刺激是一种基于电磁感应，利用磁场快速变化调节神经元兴奋性的非侵入性神经刺激技术，常用于神经系统疾病的治疗，可以改

善帕金森病运动症状。功能影像学研究发现,作用于右后颞上回的重复经颅磁刺激可以促进帕金森病患者口面部感觉运动皮质和尾状核激活,并增加这些区域与刺激区域的功能连接,同时增加颞叶听觉反馈区与腹侧前运动区之间的白质纤维束完整性,从而改善构音障碍[86-88]。连续θ爆发式刺激是一种特殊形式的重复经颅磁刺激,可用于治疗帕金森病构音障碍[89]。(2)语音训练:药物治疗、手术治疗及重复经颅磁刺激对帕金森病构音障碍的作用并不明确,语音训练则是目前的有效治疗方法[90],包括多种治疗范式,其中励-协夫曼言语治疗(LSVT)是一种着重于重新校准声音强度、增加声音振幅以及重新训练平均声音强度的感知和内部反馈以产生和维持治疗效果的高强度规范性干预措施[91],可改善帕金森病患者构音功能相关脑区的异常激活[92]。LSVT包括LSVT-LOUD和LSVT-ARTIC两分支,分别侧重声音强度和语音清晰度,均可改善帕金森病构音障碍[87,93-94],治疗后1和7个月时LSVT-LOUD较LSVT-ARTIC对客观声学指标和主观量表评分的改善效果更显著[91]。功能影像学研究发现,LSVT-LOUD治疗后左侧前运动区和双侧听觉皮质激活增强,且治疗后7个月左侧皮质运动区和左侧听觉皮质激活增强与客观声学指标的改善相关,而LSVT-ARTIC治疗后虽双侧运动前皮质和左侧岛叶皮质激活增强,但与客观声学指标无显著关联性[95];且LSVT-LOUD治疗后构音功能改善可在较长时间内仍保持良好[91],可能与LSVT-LOUD改善自上而下的言语运动网络调节能力有关[96]。LSVT治疗有效程度与发音期间右前岛叶皮质、右侧基底节和右侧背外侧前额皮质兴奋性呈正相关,与皮质运动区和前运动区兴奋性呈负相关[90]。上述研究为LSVT治疗帕金森病听觉反馈障碍提供了神经行为学证据。

综上所述,帕金森病构音障碍病理生理学机制复杂,且与运动障碍发病机制存在一定差异。未来尚待多中心大样本研究进一步探究帕金森病构音障碍发病机制、严重程度和亚型评估方法、治疗方案,以提供个体化治疗。此外,由于构音障碍可能与帕金森病临床前期有关,尽早发现对提供及时的神经保护具有重要意义[5-7]。同时,应开发新技术如计算机神经网络学习、智能手机应用程序等,实时远程收集数据早期发现并监测疾病进展以提供更适宜的治疗方案[97-98]。

利益冲突 无

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