·专题综述·

帕金森病相关认知功能障碍

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【摘要】 帕金森病认知功能障碍起病隐匿，是帕金森病常见非运动症状，包括帕金森病轻度认知损害和帕金森病痴呆，尤以执行功能障碍突出，亦可见视空间能力、记忆力和言语功能等认知域损害。主要危险因素包括男性、高龄、低受教育程度、严重运动症状、基线认知功能较差和白天过度嗜睡。主要病理改变是脑组织路易小体形成，也可见阿尔茨海默病样病理改变。脑脊液总α-突触核蛋白和β-淀粉样蛋白1～42水平降低作为生物学标志物的价值尚存争议。相关基因研究较少且无法获得肯定结论。PET显像发现多巴胺能通路和乙酰胆碱能通路均参与帕金森病认知功能障碍的发生；MRI研究发现皮质及皮质下结构萎缩与帕金森病认知功能障碍有关。嗅觉障碍可能是帕金森病认知功能障碍的预测因素之一。帕金森病痴呆与路易体痴呆具有共同的生物学特性，二者鉴别诊断困难。胆碱酯酶抑制剂和美金刚有助于改善临床症状，应注意个体化治疗。认知行为疗法具有潜在临床价值，尚待更多研究。

【关键词】 帕金森病； 认知障碍； 综述

Cognitive impairment in Parkinson´s disease

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【Abstract】 Parkinson´s disease cognitive impairment (PD-CI) is one of the major non-motor symtoms (NMS) of PD, including Parkinson´s disease with mild cognitive impairment (PD-MCI) and Parkinson´s disease dementia (PDD). Executive dysfunction is relatively prominent, but other cognitive domains as visuospatial ability, memory and language can also be affected. Main risk factors for PD-CI include male gender, advanced age, low education, severe motor symptoms, low baseline cognitive function and excessive daytime sleepiness (EDS). Lewy bodies are main pathological changes, and Alzheimer´s disease (AD) related pathological changes can also be seen. The application value of decreased α-synuclein (α-Syn) and β-amyloid 1–42 ($A\beta_{1-42}$) levels in cerebrospinal fluid (CSF) as biomarkers remains controversial. There are few related research and no defined pathogenic genes currently. Both dopaminergic pathway and acetylcholinergic pathway are involved in the occurrence of PD-CI as demonstrated in PET studies. Cortical and subcortical atrophy are associated with PD-CI as observed in MRI studies. Olfactory dysfunction may be one of the predictors of cognitive impairment. PDD and dementia with Lewy bodies (DLB) share common biological characteristics, therefore the differential diagnosis sometimes is difficult. Cholinesterase inhibitors (ChEIs) and memantine help to improve clinical symptoms, but treatment decision should be made with individualization. Cognitive behavioral treatment (CBT) has potential clinical value and should be investigated by more studies.

【Key words】 Parkinson disease; Cognition disorders; Review

帕金森病(PD)非运动症状(NMS)严重影响患者生活质量、增加照料者负担，近年来逐渐引起人们关注。帕金森病认知功能障碍是帕金森病常见非运动症状，包括帕金森病轻度认知损害(PD-MCI)和帕金森病痴呆(PDD)。研究显示，帕金森病痴呆8年累积患病率高达78.2%[1]。约40%帕金森病患者疾病早期即可出现帕金森病轻度认知损害，增加其进展为帕金森病痴呆的风险[2-5]。因此，了解帕金森病轻度认知损害和帕金森病痴呆相关临床表

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现和生物学标志物，对阐明二者病理生理学机制和早期诊断与治疗具有重要意义。

一、临床表现

帕金森病认知功能障碍起病隐匿，执行功能障碍相对突出，亦可见视空间能力、记忆力和言语功能等认知域损害。帕金森病轻度认知损害患者可以存在单个或多个认知域损害，执行功能和记忆功能障碍最早出现且最突出，二者发生率相似，亦有研究显示，执行功能障碍发生率高于记忆障碍[6-7]。帕金森病痴呆患者执行功能、视觉和视空间能力障碍相对突出且较阿尔茨海默病（AD）患者严重，但词语记忆力、视觉记忆力和言语功能障碍较阿尔茨海默病患者轻微，这些差异在认知功能障碍早期或中期相对明显，至疾病晚期则难以区分严重认知功能障碍。因此，早期进行神经心理学测验可以为临床诊断提供重要客观证据，但在鉴别诊断方面的作用有限。帕金森病痴呆患者精神症状发生率和严重程度较路易体痴呆（DLB）轻微，存在认知功能障碍的帕金森病患者更易出现抑郁、焦虑和淡漠等情感异常[8]。

目前认为，帕金森病认知功能障碍的预测因素包括男性、高龄、低受教育程度、严重运动症状、基线认知功能较差和白天过度嗜睡（EDS），而与震颤严重程度无关联性[9-12]。此外，帕金森病认知功能障碍除考虑与原发病相关外，还应排除药物对认知功能和行为的不良反应[13]。

二、生物学标志物

1. 病理学和脑脊液标志物　帕金森病痴呆患者主要病理改变是脑组织路易小体（LB）形成，由α-突触核蛋白（α-Syn）组成[14]。病理学研究显示，大脑皮质路易小体数目与认知功能障碍严重程度和帕金森病痴呆密切相关[15]。值得注意的是，并非所有存在大脑皮质路易小体的帕金森病患者均发生痴呆，帕金森病痴呆患者亦常见阿尔茨海默病典型病理改变——神经炎性斑［NPs，又称老年斑（SPs）］和神经原纤维缠结（NFT）。大脑皮质路易小体与阿尔茨海默病病理改变具有相关性，细胞模型研究结果显示，α-Syn可以促进tau蛋白和β-淀粉样蛋白（Aβ）沉积[15]。帕金森病和阿尔茨海默病早期均可以发生Meynert基底核变性，使胆碱能通路受阻，胆碱能活性下降与认知功能尤其是记忆功能减退密切相关[16]。研究显示，帕金森病痴呆和路易体痴呆患者脑脊液总α-Syn水平下降[17]，尽管其临床价值尚存争议，但该项指标对反映帕金森病认知功能障碍的神经病理改变可能有一定价值[18]。此外，帕金森病轻度认知损害和帕金森病痴呆患者也可以观察到脑脊液可溶性$A\beta_{1\sim42}$水平下降，与帕金森病早期认知功能障碍相关[19]，因此认为，帕金森病痴呆是两种病理学机制共同作用的结果[20]。

2. 基因学标志物　不同基因型可能影响认知功能，但与帕金森病认知功能障碍之间的相关性尚未完全阐明。关于多巴胺能通路相关靶点的基因学研究较多，例如，与大脑皮质多巴胺表达相关的儿茶酚-O-甲基转移酶（*COMT*）基因[21]、与纹状体多巴胺再摄取相关的溶质转运体-多巴胺转运体1（*SLC6A3/DAT1*）基因[22]，这些基因异常可能与帕金森病患者额叶-纹状体通路功能异常有关。胆碱能通路在帕金森病认知功能障碍中发挥重要作用[23]，但是关于胆碱能通路相关靶点的基因学研究较少，目前仅见编码烟碱型乙酰胆碱受体α4亚单位（*CHRNA4*）基因，但并未显示其与老龄化相关[24]。Bohnen等[23]认为，多巴胺能通路和胆碱能通路的不同基因之间可能存在交互作用。某些阿尔茨海默病相关基因也可能参与帕金森病痴呆的发生，一项前瞻性临床研究显示，微管相关tau蛋白（*MAPT*）基因*H1/H2*基因型和载脂蛋白Eε4（*ApoEε4*）等位基因均与帕金森病痴呆发生率相关[25]；亦有学者持反对观点质疑其相关性[26]。研究显示，基于家族性帕金森病的α-突触核蛋白基因（*SNCA*）E64点突变[27-28]和三重扩增[29]以及葡糖脑苷脂酶（*GBA*）基因[30]均与帕金森病认知功能障碍及其严重程度相关。总之，帕金森病认知功能障碍相关基因研究较少且涉及不同神经生化通路，尚无法获得肯定结论。

3. 影像学标志物　（1）PET显像：^{18}F-脱氧葡萄糖（^{18}F-FDG）PET研究显示，帕金森病轻度认知损害患者主要表现为局限性额叶、颞叶和海马旁回葡萄糖代谢降低，帕金森病痴呆患者表现为双侧额叶、顶叶后部和枕叶葡萄糖代谢明显降低[31]，提示帕金森病患者大脑皮质中后部葡萄糖低代谢可能与认知功能障碍相关，代谢降低越明显、认知功能障碍越严重，表明^{18}F-FDG PET可以为早期识别帕金森病认知功能障碍提供有价值的影像学信息。^{18}F-多巴胺（^{18}F-Dopa）PET研究显示，与正常对照者相比，帕金森病痴呆患者和帕金森病非痴呆患者纹状体多巴胺合成减少，尾状核^{18}F-Dopa摄取减少，与工作记忆和执行功能减退相关[32]。一项采用^{11}C-雷氯必

利(^{11}C-RAC)PET检测执行认知任务时多巴胺释放的研究结果显示,与正常对照者相比,帕金森病非痴呆患者执行空间相关任务时尾状核背侧多巴胺释放减少[33],提示黑质-纹状体多巴胺减少在帕金森病患者执行功能障碍中发挥重要作用。另一项采用高亲和性纹状体外多巴胺D2/D3受体对比剂^{11}C-FLB 457 PET的研究显示,执行认知任务时,正常对照者右侧眶额皮质多巴胺释放增加,而帕金森病患者并未观察到此种现象[34]。上述研究均提示,帕金森病认知功能障碍的发病机制不仅是由于黑质-纹状体变性,还与中脑多巴胺能通路有关。胆碱能通路亦参与其中,一项采用^{11}C-甲基-哌啶-4-丙酸(^{11}C-PMP)PET检测乙酰胆碱酯酶活性的研究显示,帕金森病痴呆患者较非痴呆患者、帕金森病非痴呆患者较正常对照者脑组织乙酰胆碱酯酶活性明显降低,且与注意力、工作记忆和执行功能障碍存在相关性[23]。Petrou等[35]对11项^{11}C-匹兹堡复合物B(^{11}C-PIB)PET研究进行回顾分析发现,路易体痴呆(DLB)患者较帕金森病痴呆患者、帕金森病痴呆患者较帕金森病轻度认知损害患者Aβ沉积更明显。检测tau蛋白和神经原纤维缠结的PET对比剂,目前仅局限于阿尔茨海默病、轻度认知损害和进行性核上性麻痹(PSP)的研究,其在帕金森病轻度认知损害和帕金森病痴呆中的研究尚未见诸报道[36]。总之,通过PET显像可以反映出帕金森病认知功能障碍发生与发展的异质性。在神经递质水平,黑质-纹状体和中脑多巴胺能通路以及乙酰胆碱能通路均可能参与帕金森病认知功能障碍的发生且作用机制复杂;在分子病理学水平,Aβ、tau蛋白和α-Syn在帕金森病认知功能障碍发生中的作用机制也可能不同,因此尚待更大规模的研究进一步加以验证。(2)MRI:帕金森病认知功能障碍的诊断主要依靠临床表现,MRI仅能提供支持证据。过去10年的MRI研究比较帕金森病痴呆或非痴呆患者与正常对照者的脑结构变化,得出以下结论。首先,多项横断面和前瞻性研究根据认知功能将帕金森病患者分组,与正常对照者相比,帕金森病非痴呆患者未见明显脑萎缩[37-39]。其次,有研究显示,与正常对照者和帕金森病非痴呆患者相比,帕金森病痴呆患者海马、海马旁回、枕叶、右侧额叶、左侧顶叶灰质体积缩小,尤以枕叶萎缩更为明显[40]。亦有研究显示,帕金森病痴呆患者左侧颞上回、右侧海马或前额叶背外侧皮质、前扣带回、颞叶,以及皮质下海马、丘脑、尾状核萎缩更加突出[41]。有研究比较帕金森病轻度认知损害患者与正常对照者脑萎缩程度,结果显示,前者辅助运动区(SMA)、颞上回、顶叶上部皮质和枕叶内侧皮质萎缩速度更迅速[38]。不同脑结构的解剖学改变可能与不同认知域损害有关,大脑皮质辅助运动区萎缩是提示帕金森病轻度认知损害的潜在影像学标记[30]。颞叶萎缩见于帕金森病痴呆及其他类型痴呆,可能并非是帕金森病认知功能障碍的影像学标记。帕金森病痴呆患者枕叶萎缩较非痴呆患者明显,且与幻觉密切相关,可能是帕金森病轻度认知损害患者出现幻觉的影像学标记[42]。总之,皮质及皮质下结构萎缩与帕金森病认知功能障碍有关。

4.嗅觉障碍 帕金森病患者嗅觉障碍发生率为50%~90%[43-44],且是疾病早期表现之一。从病理学机制看,嗅球和低位脑干是最早出现α-Syn的部位,此后再向脑干上部和大脑皮质扩散。嗅觉检测简便、费用较低,故成为有价值的生物学标记。一项前瞻性队列研究显示,约91%帕金森病患者在诊断时即已存在不同程度嗅觉障碍;基线嗅觉减退与非运动症状和认知功能减退相关,若同时存在脑脊液$A\beta_{1\sim42}$水平下降,提示帕金森病轻度认知损害风险增加[45],提示嗅觉障碍可能是帕金森病非运动症状和认知功能障碍的预测因素之一。

三、鉴别诊断

帕金森病痴呆与路易体痴呆具有共同的生物学特性,典型病理改变均可见α-Syn[46],临床表现存在重叠,故二者鉴别诊断较为困难。目前主要依据运动症状与认知功能障碍的时间关系制定“一年规则(1-year rule)”,即运动症状出现前后1年内发生认知功能障碍,诊断为路易体痴呆,反之则诊断为帕金森病痴呆[47],但“一年规则”具有主观性。与二者区别相比,二者之间的联系更加广泛:路易体痴呆患者认知功能障碍与运动症状在时间上密切相关,而帕金森病患者也常于疾病早期出现认知功能障碍;临床表现均为精神症状、自主神经功能障碍、快速眼动睡眠期行为障碍(RBD)、认知功能波动和对抗精神药敏感等;神经心理学测验均可见注意障碍、执行功能障碍、视空间能力障碍、言语障碍、记忆障碍和行为改变。然而,二者的确存在细微差别,路易体痴呆患者的幻觉和对抗精神药的敏感性较帕金森病痴呆患者更明显,帕金森样症状相对轻微;而帕金森病痴呆患者的运动症状则表现为更多

的不对称性。目前更倾向于不必要对二者进行严格区分。

四、治疗原则

1. 药物治疗　主要是对症治疗，目前尚无改变疾病进程的药物。帕金森病痴呆和路易体痴呆存在胆碱能通路缺陷已获共识[48-49]，因此，胆碱酯酶抑制剂可能有助于改善临床症状，但易出现震颤加重和胃肠道不良反应。为期24周的随机双盲安慰剂对照临床试验显示，与安慰剂组相比，卡巴拉汀和多奈哌齐组患者阿尔茨海默病评价量表-认知分量表（ADAS-Cog）评分显著增加[50]。因此，若无明显不良反应，推荐胆碱酯酶抑制剂用于治疗帕金森病痴呆。随访观察2～3个月，若对临床症状有改善作用，推荐继续应用；若无改善，应逐渐停药，尽量避免突然停药导致的认知功能和行为恶化。研究显示，路易体痴呆患者存在谷氨酸能通路改变[51]。尽管美金刚推荐用于中至重度阿尔茨海默病和血管性痴呆（VaD），但小样本临床研究结果显示，帕金森病痴呆和路易体痴呆患者应用美金刚均可改善整体认知功能[52]，亦有加重幻觉和神经精神症状的报道[53]，因此临床应用须谨慎。Wang等[54]对10项随机对照临床试验进行Meta分析显示，基于现有证据，多奈哌齐、卡巴拉汀和美金刚均可改善整体认知功能。胆碱酯酶抑制剂在改善帕金森病痴呆患者行为症状、提高日常生活活动能力（ADL）和减轻照料者负担方面的作用更加突出，3种药物安全性均较好，对运动症状无明显影响。帕金森病患者常出现幻视和妄想等精神症状，尤其是疾病晚期阶段，抗帕金森病药不良反应敏感，因此，应适当调整药物剂量。抗胆碱能药易出现精神症状，应首先考虑停药。若无法停用导致精神症状的抗帕金森病药时，应考虑减量。需要药物控制精神症状时，推荐小剂量喹硫平和氯氮平，但应警惕运动症状加重以及心血管事件和死亡风险[55]。

2. 认知行为疗法　由于个体认知储备不同，认知功能改变也不尽相同。认知行为疗法（CBT）可以提高认知储备，提供神经保护和修复方面的获益，但相关证据尚不充足[56]。认知行为疗法主要包括认知刺激和认知训练。认知刺激通过受试者参加一系列群体活动和讨论，提高认知功能和社会功能。认知训练强调在专业指导下完成一套可以反映特定认知功能的任务，如记忆力、注意力、解决问题能力，或者在专业指导下练习提高记忆力的方法，如轨迹或视觉想象。研究显示，计算机辅助认知功能训练有助于提高帕金森病患者注意力、信息处理速度、执行功能、词语流畅性和视空间能力，其机制可能是通过训练改变脑结构和功能[57]。目前关于帕金森病认知功能障碍患者认知行为疗法的相关研究仍较少，随着对疾病认识的深入，亟待相关研究探索改善帕金森病认知功能的方法。

综上所述，帕金森病认知功能障碍相关生物学标志物，如神经心理学测验、基因和脑脊液标志物、结构性和功能性影像学标志物，以及嗅觉检测，有助于阐明疾病发病机制、早期诊断和及时治疗。尽管目前尚缺乏针对性的疾病修正治疗（DMT），但胆碱酯酶抑制剂和美金刚有助于改善临床症状，应用时应注意个体化治疗。认知行为疗法具有潜在的临床价值，尚待更多研究。

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下期内容预告 本刊2017年第7和8期报道专题为神经遗传性疾病，重点内容包括：关于临床判断致病性突变和无害突变的思考，浅谈神经遗传性疾病基因诊断策略与问题，肢带型肌营养不良症诊断与治疗进展，面-肩-肱型肌营养不良症分子学机制研究进展，腓骨肌萎缩症治疗进展，脑组织铁沉积性神经变性病遗传学研究进展，原发性家族性脑钙化研究进展，基因检测在脑血管病精准治疗中的应用，帕金森病伴疼痛机制研究进展，特发性震颤研究进展，遗传性周围神经病影像学研究进展，应用目标区域测序技术快速诊断腓骨肌萎缩症，维生素B_{12}依赖型甲基丙二酸血症家系临床、生化、基因突变分析及疗效评价，青少年型亨廷顿病临床特征及基因突变分析，头部震颤伴小脑萎缩基因检测研究，遗传性毛细血管扩张型共济失调四例，中国发作性运动诱发性运动障碍社会心理学调查研究，发作性运动诱发性运动障碍临床表型分析，脂肪酸羟化酶相关神经变性病四例，进行性肌阵挛癫痫临床病理及基因突变分析