文章编号:1003-2754(2025)02-0133-04 doi:10.19845/j.cnki.zfysjjbzz.2025.0026

帕金森病伴周围神经病变的机制

张厚文[1], 朱 虹[1], 李春荣[2], 王钟秀[2]综述, 吴 忧[1,3]审校

摘 要: 帕金森病(PD)是第二大常见的神经系统变性疾病,病变主要累及椎体外系,由多巴胺能黑质纹状体通路的退化引起。近年来大多数研究表明PD病理及病变不仅局限于中枢,而是一种全身性、多系统疾病。PD伴有周围神经病变(PN)越来越受到人们关注,但具体发病机制目前尚不明确。PD患者运动症状常掩盖周围神经病变表现,因此,PD合并PN临床识别度不高,给临床诊治带来一定困难。本文就PD合并PN的发病机制进行综述。

关键词: 帕金森病; 周围神经病变; 机制

中图分类号:R742.5;R745 **文献标识码:**A

Mechanisms of Parkinson disease with peripheral neuropathy *ZHANG Houwen, ZHU Hong, LI Chunrong, et al.* (*The Second Clinical Medical College of Zhejiang Chinese Medical University, Hangzhou* 310053, *China*)

Abstract: Parkinson disease (PD) is the second most prevalent neurodegenerative disorder and predominantly impacts the extrapyramidal system. This condition arises from the degeneration of the dopaminergic nigrostriatal pathway. In recent years, studies have shown that PD pathology and lesions are not limited to the center nervous system, and that PD is a systemic and multisystem disease. The concurrence of PD with peripheral neuropathy (PN) has been increasingly acknowledged, although its pathogenesis remains elusive. The motor symptoms in PD patients often mask the symptoms of PN, leading to relatively low clinical recognition of PD coexisting with PN. This poses challenges in the clinical diagnosis and treatment of PD. This review comprehensively summarize the pathogenesis of PD coexisting with PN.

Key words: Parkinson disease; Peripheral neuropathy; Mechanism

帕金森病(Parkinson disease, PD)是中老年人群常见的神经变性疾病。由于α-突触核蛋白(α-synuclein,α-syn)的异常聚集和黑质多巴胺能神经元丢失导致的运动症状和非运动症状,临床上主要以静止性震颤、运动迟缓、肌强直、姿势平衡障碍等运动症状为主要特征[1]。PD非运动症状如认知障碍、肢体麻木、疼痛、便秘、排尿障碍等近些年逐渐受到重视,而这些可能与PD周围神经病变(peripheral neuropathy,PN)相关[2]。自1991年Bulling等[3]通过神经传导速度检查首次发现PD患者存在PN后,随着检查手段的发展,PD患者合并周围神经损伤、变性逐渐受到关注。研究发现,与一般人群相比,PD患者的PN患病率增加了2.4倍[4],但其病变机制存在争议。本文就PD合并PN的类型及机制研究进行整理总结,阐述如下。

1 临床表现及神经电生理改变

1.1 急性和亚急性周围神经病变 4周内出现类似吉兰-巴雷综合征或急性炎性神经病变的临床表现和(或)神经电生理参数迅速恶化定义为急性周围神经病变[5,6]。主要临床表现为四肢肌力降低,针刺觉减退,肌腱反射及振动阈值消失,患者症状迅速进展,常在7 d内达到最低点[5,7]。临床表现类似于吉兰-巴雷综合征的急性或亚急性周围神经病的病例相继被报道。2009年Rajabally等[8]首次报道了1例在空肠弯曲杆菌感染后发展为急性运动轴索神经病的病例。随后,2014年1例在输注左旋多巴治疗期间发生急性炎症性脱髓鞘性多发性神经病伴有神经节苷脂抗体阳性的患者被报道[9]。Urbant等[5,6]报道了2例在接受左旋多巴治疗期间发生维生素B_{12}和维生素B_6缺乏的PD患者发展为亚急性神经轴索病变。急性周围神经病变可同时存在轴索和脱髓鞘损伤,肌电图显示感觉神经动作电位消失,运动传导速度减慢,<正常值下限的70%,F波潜伏期延长。

1.2 慢性周围神经病变 慢性对称性远端小纤维受累如感觉异常、感觉减退或下肢疼痛是PD周围神经损伤的临床表现[10]。根据Müller等[11]的研究,在PD患者中,腓肠神经的神经传导速度可能明显低于正常水平,这表明存在髓鞘损伤。在Ceravolo

收稿日期:2024-06-25;**修订日期:**2024-12-05

基金项目:浙江省卫生健康科技计划(2021KY841)

作者单位:(1.浙江中医药大学第二临床医学院,浙江 杭州 310053;2.浙江省人民医院神经内科,浙江 杭州 310014;3.浙江中医药大学附属第二医院神经内科,浙江 杭州 310005)

通信作者:吴 忧,E-mail:20071023@zcmu.edu.cn

等[12]研究显示，PD患者的肌电图检查显示出运动单位电位的显著改变，如振幅增加和多相性增多，是神经轴突损伤和肌肉重排的迹象。根据Zis等[13]研究，PD患者可能表现出感觉神经电位的减弱或消失，反映了感觉纤维的损伤。Hovaguimian等[14]研究表明，在PD患者中，定量感觉测试可以揭示对温度和触觉刺激的异常感觉阈值，表明小纤维神经存在损伤。

2　发病机制

2.1　药物治疗在神经损伤中的作用　左旋多巴是PD的主要药物治疗方法，能够有效纠正多巴胺缺失的问题[15]。虽然它在改善PD的运动症状方面具有重要价值，但是长期使用可能会导致维生素B族的代谢紊乱[12]。有研究显示，长期接受左旋多巴/卡比多巴治疗的PD患者，血浆维生素B_6、维生素B_{12}水平普遍偏低[16]。这种代谢紊乱可能是由于左旋多巴的代谢过程中消耗了这些维生素，或者左旋多巴及其代谢产物间接影响了肠道对这些维生素的吸收，与PN严重程度相关[17-19]。而这些维生素不仅参与神经传递物质的合成，还是神经髓鞘形成的必需因子[20]。因此，维生素缺乏可能导致神经髓鞘的脱髓鞘，进而影响神经传导速度，引发周围神经病变。

2.2　代谢异常和氧化应激的关系　在PD中，代谢异常表现为同型半胱氨酸和甲基丙二酸水平升高[21-23]。一项研究通过比较60例PD患者的电流感知阈值和血浆中的生化指标，发现长期LD暴露增加了Aδ和C神经纤维受损的风险，并与同型半胱氨酸升高和甲基丙二酸水平升高相关[24]。另一项研究在154例PD患者中发现31.8%存在PN，与疾病持续时间、LD累计剂量和同型半胱氨酸水平紧密相关[25]。这些代谢物水平的升高可能直接是维生素B_{12}和B_6缺乏的结果[26,27]。同型半胱氨酸的增加与氧化应激增加密切相关，这可能导致线粒体功能障碍和神经细胞的氧化损伤[28,29]。氧化应激在PD的神经变性过程中起着关键作用，尤其是在多巴胺能神经元的损害中[30]。因此，代谢异常不仅会加剧中枢神经系统的损伤，还可能是周围神经病变的关键因素。

2.3　遗传易感性与神经损伤　特定的遗传变异，如*Parkin*和*MTHFR*基因的变异与PD患者中PN的发展相关[31,32]。研究显示，带有*Parkin*突变的患者神经元显示出线粒体生物发生途径的缺陷，导致mtDNA稳态失衡，能量传感器sirtuin 1下调，以及促炎细胞因子过表达[33,34]。曾有病例报道，*MTHFR*基因突变PD患者，存在持续性高同型半胱氨酸血症[35]，可能与其同名编码亚甲基四氢叶酸还原酶相关。这种遗传易感性表明，在PD的发病机制中，除了中枢神经系统的变化外，外周神经系统也可能受到影响。

2.4　线粒体功能障碍与能量代谢　PD患者中的线粒体功能障碍可能导致能量代谢异常[36,37]。线粒体是细胞内的能量工厂，其功能障碍可能导致ATP产生减少，进而影响神经细胞的能量供应。神经细胞尤其是神经末梢对能量供应非常敏感，能量供应不足可能导致神经传导功能障碍和神经纤维的结构损伤[38]。此外线粒体DNA（mtDNA）损伤可引发过度I型干扰素反应、线粒体自噬失败、内质网-线粒体通信障碍和线粒体活性氧（mitochondrial reactive oxygen species，mtROS）的产生促进神经炎症反应[39]。

2.5　α-突触核蛋白沉积　PD的另一个特征是大脑中α-syn的异常沉积。有研究发现，在几乎所有的PD患者皮肤神经纤维中可见磷酸化α-syn沉积物[40-42]。通过影像学、尸检、结肠镜活检等在骶副交感神经核、食道肌间丛、交感神经节、迷走神经、肠神经系统等中也发现了胆碱能神经元缺失以及大量的磷酸化α-syn，这可能与PN的发展有关[43-47]。α-syn在周围神经系统中的聚集可能导致神经纤维结构和功能的损害，影响神经信号的传递。

2.6　免疫炎症反应　对PD患者外周血和脑脊液的大量研究表明，炎症标志物和免疫细胞群发生了改变。研究表明促炎细胞因子肿瘤坏死因子（tumor necrosis factor，TNF）、干扰素-γ（interferon-γ，IFNγ）、白细胞介素-1β（interleukin-1β，IL-1β）、白细胞介素-6（interleukin-6，IL-6）、白细胞介素-2（interleukin-2，IL-2）、CXC趋化因子配体8（cysteine X chemokine ligand 8，CXCL8）和趋化因子配体2（C-C motif chemokine ligand 2，CCL2）的水平在PD患者的血清中升高，并与疾病严重程度和残疾相关[48]。这些改变可能引发或加剧神经炎症并使神经变性过程持续存在，可能会给周围神经系统带来额外的损伤[48,49]。免疫细胞的激活和炎症因子的释放可能会导致神经纤维的受损和退化。这种炎症反应可能与PD的病理过程相关，也可能与长期药物治疗和慢性应激反应有关。

3 总结与展望

当前的研究主要集中在探讨PD患者中PN的电生理学特征、临床表现以及可能的病理机制。这些研究揭示了PD中PN的多种性质，包括神经传导速度变化、肌电图异常特征、感觉神经反应改变，以及通过定量感觉测试观察到的感觉阈值变化。

尽管PD合并PN取得了一些进展，但病理机制仍不完全清楚，需要更深入的研究。未来的研究工作应集中在以下几个方面：(1)发展用于早期诊断和监测PD中PN进展的生物标志物，可能包括血液或脑脊液中的特定蛋白质或代谢产物。(2)通过分子生物学和神经生化研究了解PD中PN的病理机制，特别是关于线粒体功能障碍、遗传易感性以及免疫炎症反应如何影响神经系统的细节。(3)开发针对PD中PN的特定治疗方法，如新的药物治疗、营养补充治疗或神经修复疗法。(4)利用大数据分析方法，整合临床数据和电生理学数据，以更好地理解PD中PN的全貌并指导临床治疗。(5)进行长期随访研究，以观察PD患者中PN的自然病程和响应不同治疗策略的情况。PD伴有PN是一个复杂且多面的问题，给PD的研究和治疗带来新的挑战。

利益冲突声明：所有作者均声明不存在利益冲突。

作者贡献声明：张厚文、朱虹负责设计论文框架、查阅文献并起草论文；李春荣负责查阅文献；王钟秀负责论文修改；吴忱负责拟定写作思路、指导撰写论文并最后定稿。

[参考文献]

[1] Bloem BR, Okun MS, Klein C. Parkinson's disease[J]. Lancet, 2021, 397(10291): 2284-2303.

[2] Merola A, Rosso M, Romagnolo A, et al. Peripheral neuropathy as marker of severe Parkinson's disease phenotype[J]. Mov Disord, 2017, 32(8): 1256-1258.

[3] Bulling MT, Wing LM, Burns RJ. Controlled release levodopa/carbidopa (Sinemet CR4) in Parkinson's disease: an open evaluation of efficacy and safety[J]. Aust N Z J Med, 1991, 21(4): 397-400.

[4] Conradt C, Guo D, Miclea A, et al. Increased prevalence of polyneuropathy in Parkinson's disease patients: an observational study [J]. J Parkinsons Dis, 2018, 8(1): 141-144.

[5] Mancini F, Comi C, Oggioni GD, et al. Prevalence and features of peripheral neuropathy in Parkinson's disease patients under different therapeutic regimens[J]. Parkinsonism Relat Disord, 2014, 20(1): 27-31.

[6] Uncini A, Eleopra R, Onofrj M. Polyneuropathy associated with duodenal infusion of levodopa in Parkinson's disease: features, pathogenesis and management[J]. J Neurol Neurosurg Psychiatry, 2015, 86(5): 490-495.

[7] Szadejko K, Dziewiatowski K, Szabat K, et al. Polyneuropathy in levodopa-treated Parkinson's patients[J]. J Neurol Sci, 2016, 371: 36-41.

[8] Rajabally YA, Ramlackhansingh A, Fraser M, et al. Neuroleptic malignant syndrome and acute motor axonal neuropathy after Campylobacter jejuni infection[J]. Neurophysiol Clin, 2009, 39(3): 135-138.

[9] Galazky I, Schoof J, Stallforth S, et al. Guillain-Barré/CIDP-like neuropathy in two parkinsonian patients following intestinal levodopa/carbidopa treatment[J]. Parkinsonism Relat Disord, 2014, 20(1): 125-127.

[10] Grofik M, Sivák Š, Nosáľ V, et al. The influence of levodopa, entacapone and homocysteine on prevalence of polyneuropathy in patients with Parkinson's disease[J]. J Neurol Sci, 2018, 392: 28-31.

[11] Müller T, van Laar T, Cornblath DR, et al. Peripheral neuropathy in Parkinson's disease: Levodopa exposure and implications for duodenal delivery[J]. Park Relat Disord, 2013, 19(5): 501-507.

[12] Ceravolo R, Cossu G, di Poggio MB, et al. Neuropathy and levodopa in Parkinson's disease: evidence from a multicenter study [J]. Mov Disord, 2013, 28(10): 1391-1397.

[13] Zis P, Grünewald RA, Chaudhuri RK, et al. Peripheral neuropathy in idiopathic Parkinson's disease: a systematic review[J]. J Neurol Sci, 2017, 378: 204-209.

[14] Hovaguimian A, Gibbons CH. Diagnosis and treatment of pain in small-fiber neuropathy [J]. Curr Pain Headache Rep, 2011, 15(3): 193-200.

[15] LeWitt PA. Levodopa therapy for Parkinson's disease: Pharmacokinetics and pharmacodynamics[J]. Mov Disord, 2015, 30(1): 64-72.

[16] Rojo-Sebastián A, González-Robles C, de Yébenes JG. Vitamin B6 deficiency in patients with Parkinson disease treated with levodopa/carbidopa [J]. Clin Neuropharmacol, 2020, 43(5): 151-157.

[17] Vanta OM, Tohanean N, Pintea S, et al. Large-fiber neuropathy in Parkinson's disease: clinical, biological, and electroneurographic assessment of a Romanian cohort[J]. J Clin Med, 2019, 8(10): 1533.

[18] Loens S, Chorbadzhieva E, Kleimann A, et al. Effects of levodopa/carbidopa intestinal gel versus oral levodopa/carbidopa on B vitamin levels and neuropathy[J]. Brain Behav, 2017, 7(5): e00698.

[19] Andréasson M, Brodin L, Laffita-Mesa JM, et al. Correlations between methionine cycle metabolism, COMT genotype, and polyneuropathy in L-dopa treated Parkinson's disease: a preliminary cross-sectional study[J]. J Parkinsons Dis, 2017, 7(4): 619-628.

[20] McGarel C, Pentieva K, Strain JJ, et al. Emerging roles for folate and related B-vitamins in brain health across the lifecycle [J]. Proc Nutr Soc, 2015, 74(1): 46-55.

[21] Toth C, Breithaupt K, Ge S, et al. Levodopa, methylmalonic acid, and neuropathy in idiopathic Parkinson disease [J]. Ann Neurol, 2010, 68(1): 28-36.

[22] Ahlskog JE. Levodopa, homocysteine and Parkinson's disease: What's the problem? [J]. Parkinsonism Relat Disord, 2023, 109: 105357.

[23] Park JS, Park D, Ko PW, et al. Serum methylmalonic acid correlates with neuropathic pain in idiopathic Parkinson's disease [J]. Neurol Sci, 2017, 38(10): 1799-1804.

[24] Xiong YT, Liu MH, Gu HY, et al. Fiber selectivity of peripheral neuropathy in patients with Parkinson's disease [J]. Acta Neurol Scand, 2022, 146(1): 75-81.

[25] Ramachandran A, Jose J, Gafoor VA, et al. Prevalence and risk factors of peripheral neuropathy in Parkinson's disease [J]. Ann Indian Acad Neurol, 2022, 25(6): 1109-1115.

[26] Müller T, Riederer P. The vicious circle between homocysteine, methyl group-donating vitamins and chronic levodopa intake in Parkinson's disease [J]. J Neural Transm, 2024, 131(6): 631-638.

[27] Phokaewvarangkul O, Bhidayasiri R, Garcia-Ruiz P, et al. Homocysteine, vitamin B metabolites, dopamine-substituting compounds, and symptomatology in Parkinson's disease: clinical and therapeutic considerations [J]. J Neural Transm (Vienna), 2023, 130(11): 1451-1462.

[28] Kaur B, Sharma PK, Chatterjee B, et al. Defective quality control autophagy in Hyperhomocysteinemia promotes ER stress and consequent neuronal apoptosis through proteotoxicity [J]. Cell Commun Signal, 2023, 21(1): 258.

[29] Zhang S, Lv Y, Luo X, et al. Homocysteine promotes atherosclerosis through macrophage pyroptosis via endoplasmic reticulum stress and calcium disorder [J]. Mol Med, 2023, 29(1): 73.

[30] Bustamante-Barrientos FA, Luque-Campos N, Araya MJ, et al. Mitochondrial dysfunction in neurodegenerative disorders: Potential therapeutic application of mitochondrial transfer to central nervous system-residing cells [J]. J Transl Med, 2023, 21(1): 613.

[31] Paul DA, Qureshi ARM, Rana AQ. Peripheral neuropathy in Parkinson's disease [J]. Neurol Sci, 2020, 41(10): 2691-2701.

[32] Abbruzzese G, Pigullo S, Schenone A, et al. Does parkin play a role in the peripheral nervous system? A family report [J]. Mov Disord, 2004, 19(8): 978-981.

[33] Fakih R, Sauvé V, Gehring K. Feedforward activation of PRKN/parkin [J]. Autophagy, 2023, 19(2): 729-730.

[34] Wasner K, Smajic S, Ghelfi J, et al. Parkin deficiency impairs mitochondrial DNA dynamics and propagates inflammation [J]. Mov Disord, 2022, 37(7): 1405-1415.

[35] Reffo A, Gabelli C. Hyperhomocysteinemia and dementia associated with severe cortical atrophy, but no amyloid burden [J]. J Geriatr Psychiatry Neurol, 2022, 35(1): 57-61.

[36] Schapira AHV, Patel S. Targeting mitochondria for neuroprotection in Parkinson disease [J]. JAMA Neurol, 2014, 71(5): 537-538.

[37] Xia X, Li H, Xu X, et al. Facilitating pro-survival mitophagy for alleviating Parkinson's disease via sequence-targeted lycopene nanodots [J]. ACS Nano, 2023, 17(18): 17979-17995.

[38] Justs KA, Sempertegui S, Riboul DV, et al. Mitochondrial phosphagen kinases support the volatile power demands of motor nerve terminals [J]. J Physiol, 2023, 601(24): 5705-5732.

[39] de Oliveira LG, Angelo YS, Iglesias AH, et al. Unraveling the link between mitochondrial dynamics and neuroinflammation [J]. Front Immunol, 2021, 12: 624919.

[40] Donadio V, Incensi A, Leta V, et al. Skin nerve α-synuclein deposits: a biomarker for idiopathic Parkinson disease [J]. Neurology, 2014, 82(15): 1362-1369.

[41] Doppler K, Ebert S, Uçeyler N, et al. Cutaneous neuropathy in Parkinson's disease: a window into brain pathology [J]. Acta Neuropathol, 2014, 128(1): 99-109.

[42] Melli G, Vacchi E, Biemmi V, et al. Cervical skin denervation associates with alpha-synuclein aggregates in Parkinson disease [J]. Ann Clin Transl Neurol, 2018, 5(11): 1394-1407.

[43] Bloch A, Probst A, Bissig H, et al. Alpha-synuclein pathology of the spinal and peripheral autonomic nervous system in neurologically unimpaired elderly subjects [J]. Neuropathol Appl Neurobiol, 2006, 32(3): 284-295.

[44] Lebouvier T, Neunlist M, Bruley des Varannes S, et al. Colonic biopsies to assess the neuropathology of Parkinson's disease and its relationship with symptoms [J]. PLoS One, 2010, 5(9): e12728.

[45] Probst A, Bloch A, Tolnay M. New insights into the pathology of Parkinson's disease: does the peripheral autonomic system become central? [J]. Eur J Neurol, 2008, 15(S1): 1-4.

[46] Borghammer P, Knudsen K, Brooks DJ. Imaging systemic dysfunction in Parkinson's disease [J]. Curr Neurol Neurosci Rep, 2016, 16(6): 51.

[47] Gjerløff T, Fedorova T, Knudsen K, et al. Imaging acetylcholinesterase density in peripheral organs in Parkinson's disease with 11C-donepezil PET [J]. Brain, 2015, 138(Pt 3): 653-663.

[48] Tansey MG, Wallings RL, Houser MC, et al. Inflammation and immune dysfunction in Parkinson disease [J]. Nat Rev Immunol, 2022, 22(11): 657-673.

[49] Herrera AJ, Espinosa-Oliva AM, Oliva-Martin MJ, et al. Collateral damage: contribution of peripheral inflammation to neurodegenerative diseases [J]. Curr Top Med Chem, 2015, 15(21): 2193-2210.

引证本文:张厚文,朱　虹,李春荣,等. 帕金森病伴周围神经病变的机制[J]. 中风与神经疾病杂志,2025,42(2):133-136.