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补益肝肾汤联合美多巴治疗帕金森患者的临床效果及对认知功能的影响

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摘要 目的:探讨补益肝肾汤联合美多巴治疗帕金森(PD)患者的临床效果及对认知功能的改善作用。**方法:**选择 2012 年 3 月至 2016 年 3 月 80 例我院收治的 PD 伴轻度认知功能障碍患者并将其随机分作 2 组,对照组 40 例仅予美多巴片单药治疗,研究组 40 例在对照组的基础上另加服补益肝肾汤。治疗前后分别采用帕金森病综合评分量表(UPDRS)和简易精神量表(MMSE)对患者进行评估,评价和比较两组的疗效和不良反应的发生情况。**结果:**治疗后,研究组 UPDRS 总分明显低于对照组(P＜0.05);MMSE 评分明显高于对照组(P＜0.05);总有效率明显高于对照组(P＜0.05);不良反应发生率与对照组比较差异无统计学意义(P＞0.05)。**结论:**补益肝肾汤联合美多巴治疗 PD 患者的临床效果优于美多巴片单药治疗,并可显著改善患者的认知功能障碍,且安全性高。

关键词:补益肝肾汤;美多巴;帕金森;认知功能

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Clinical Effect of Tonify the Liver and Kidney combined with Madopar on the Parkinson's Patients and the Improvement on Cognitive Function

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ABSTRACT Objective: To explore the clinical effect of tonify the liver and kidney combined with Madopar on the parkinson's patients and improvement on the cognitive function. **Methods:** 80 cases of PD patients with mild cognitive impairment from March 2012 to March 2016 were selected and randomly divided into 2 groups, 40 cases in the control group were given Madopar tablets monotherapy, 40 cases in the research group were given tonify the liver and kidney on the basis of control group. Before and after treatment, the patients were assessed by Parkinson's Disease Rating Scale (UPDRS) and mini mental scale (MMSE), and the curative effect and incidence of adverse reaction were observed and compared between two groups. **Results:** After treatment, the total score of UPDRS in research group was significantly lower than that of the control group (P < 0.05), and the MMSE score was significantly higher than that of the control group (P < 0.05), and the total effective rate was significantly higher than that of the control group(P<0.05), but no significant difference was found in the incidence of adverse reactions between two groups (P>0.05). **Conclusions:** Tonify the liver and kidney combined with Madopar was superior to Madopar tablets monotherapy in the treatment of patients with PD, which could improve the cognitive function with high safety.

Key words: Tonify the liver and kidney; Madopar; Parkinson'sdisease; Cognitive function

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帕金森病(Parkinson's disease,PD)是因黑质纹状体系统多巴胺神经功能损害造成多巴胺与乙酰胆碱失衡的慢性神经退行性疾病。据统计,该病在我国＞65 岁人群中的发病率约 1.7%[1,2]。临床上,PD 患者常具有 4 大运动主症:静止性震颤、姿势平衡障碍、运动缓慢、肌强直。但近年研究发现,不少数的 PD 患者同时也存在一些非运动症状,且在疾病的早期即可出现,并密切影响着疾病预后,其中以认知功能障碍最常见[3,4]。有研究表明伴轻度认知功能障碍的 PD 患者发生痴呆的风险显著提高[5]。

目前,PD 尚无神经保护或重建的有效方法。美多巴能通过兴奋多巴胺受体、抑制左旋多巴含量、消除自由基而起到保护多巴胺神经元的效果,是临床治疗 PD 的常用药。中医学中并没有与 PD 或认知功能障碍相对应的中医病名,但认为二病的临床表现和转归与"颤证"或"健忘"、"呆病"等相似[6,7],故而在疾病的机理阐述或治疗上常常由此入手,并且认为二病的病因病机均与肝肾亏虚有重要联系[8]。鉴于此,本研究采用补益肝肾汤辅助美多巴治疗 PD 伴轻度认知功能障碍患者,现报道如下。

1 资料与方法

1.1 一般资料

选择 2012 年 3 月至 2016 年 3 月我院收治的 80 例 PD 伴轻度认知功能障碍患者,将其随机分为对照组和研究组,每组各 40 例。对照组中,男 23 例,女 17 例,年龄 58~79 岁,平均年

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龄 64.2± 7.2 岁,病程 3.5~6.5 年,平均病程 4.1± 1.6 年;研究组中,男 22 例,女 18 例,年龄 59~77 岁,平均年龄 64.0± 6.7 岁,病程 3~7.5 年,平均病程 4.4± 1.4 年。两组以上一般资料间比较差异无统计学意义(P>0.05),具有可比性。

1.2 入选及排除标准

入选标准:① 西医符合 " 帕金森病的诊断 "[9]标准;② 中医符合《 颤病(帕金森病) 诊疗方案》[10]诊断标准,并辨证为肝肾不足型;③ 影像学检查无明显脑器质性病变;④ 改良 Hoehn&Yahr 分级[11]为 2～4 级;⑤ 简易精神量表(MMSE)评分≥ 21 分[12];⑥ 入组前未接受过此类中药治疗;⑦ 知情同意。排除标准:① 既往有反复头外伤史或反复脑卒中发作史; ② 继发性帕金森病;③ 有药物滥用史及酗酒史;④ 伴有严重心、肺、肾功能异常;⑤ 合并其它严重中枢神经系统疾病;⑥ 伴有失语、精神病等不能配合研究;⑦ 孕妇及哺乳期妇女。

1.3 治疗方法

对照组予常规基础治疗,同时口服美多巴片(上海罗氏制药有限公司,国药准字 H10930198),开始第一周 125 mg/ 次,2 次 /d,之后每隔 7 d 加量 125 mg/d,至震颤、麻痹症状明显缓解,最大量不超过 250 mg/d,3 次 /d,连续治疗 6 个月。研究组在对照组的基础上加服补益肝肾汤:生地黄、熟地黄各 20 g,天麻、白术、黄芪、当归、威灵仙、秦艽、川芎、肉苁蓉、芍药各 10 g,防风、荆芥各 6 g、全蝎 3 g。每日 1 剂,早晚各饮服 1 次,连续治疗 6 个月。

1.4 评价工具

① 简易精神量表(mini mental state examination,MMSE)[13]:MMSE 分>21 分为轻度;10~20 分为中度;≤ 9 分为重度。② 统一帕金森病评分量表 (Unified Parkinson Disease Rating Scale,UPDRS)[15,16]:包括日常生活活动、精神行为及情绪、运动、并发症几项,评分越高表示症状越重。

1.5 观察指标

① 比较两组治疗前后的 UPDRS 评分、MMSE 评分。② 治疗前后进行一次血尿便常规、肝肾功能、心电图等检查,观察不良反应。③ 疗效评定标准[17,18]:显效:治疗前后 UPDRS 的减分>60%;④ 有效:减分 30%~60%;无效:减分<30%。

1.6 统计学方法

使用统计学软件 SPSS19.0 对数据进行分析处理, 计量资料以($\bar{x}\pm s$)表示,使用 t 检验,计数资料以%表示,使用 x^2 检验,P<0.05 为表示差异具有统计学意义。

2 结果

2.1 两组治疗前后 UPDRS 评分比较

治疗后,研究组日常生活活动、运动、并发症及总分均较治疗前明显降低 (P<0.05), 对照组以上指标虽较治疗前有所降低,但差异无统计学意义(P>0.05);研究组 UPDRS 总分明显低于对照组(P<0.05),见表 1。

表 1 两组治疗前后 UPDRS 评分比较($\bar{x}\pm s$)

Table 1 Comparison of the UPDRS scores before and after treatment between two groups($\bar{x}\pm s$)

Group	Cases	Daily life activities		Mental behavior and mood		Movement		Complication		Total score	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Research group	40	10.59± 0.77	8.22± 0.35*	1.43± 0.28	1.24± 0.85	17.75± 1.93	15.70± 1.24*	2.39± 0.51	1.19± 0.16*	33.27± 2.11	28.60± 1.16*
Control group	40	9.66± 0.94	9.05± 0.43	1.36± 0.25	1.37± 0.31	18.83± 1.44	17.07± 1.35	2.36± 0.74	2.31± 0.33	32.46± 2.09	31.90± 1.71
P	--	0.675	0.073	0.770	0.012	0.310	0.013	0.509	0.000	0.512	0.000

Note: compared with the same group before treatment*P<0.05.

2.2 两组治疗前后 MMSE 评分比较

治疗后,研究组 MMSE 评分较治疗前明显提高(P<0.05),对照组较治疗前有所降低,但差异无统计学意义(P>0.05),研究组 MMSE 评分明显高于对照组(P<0.05),见表 2。

表 2 两组治疗前后 MMSE 评分比较($\bar{x}\pm s$)

Table 2 Comparison of the MMSE scores before and after treatment between two groups($\bar{x}\pm s$)

Group	Cases	Before treatment	After treatment
Research group	40	22.27± 2.11	24.60± 2.16*
Control group	40	22.46± 2.09	21.47± 2.71
P	-	0.540	0.010

Note: compared withhe same group before treatment*P<0.05.

2.3 两组临床疗效比较

研究组总有效率为 77.5%, 明显高于对照组 [55.0%](P<0.05),见表 3。

表 3 两组临床疗效比较[n(%)]

Table 3 Comparison of the clinical efficacy between two groups[n (%)]

Group	Cases	More effective	Effective	Invalid	Total efficiency
Research group	40	9(22.5)	22(55.0)	9(22.5)	31(77.5)
Control group	40	2(5.0)	20(50.0)	18(45.0)	22(55.0)
P	-	-	-	-	＜0.05

2.4 两组不良反应发生情况的比较

两组治疗前后血尿便常规、肝肾功能、心电图等检查均正常，对照组出现 2 例恶心，1 例皮疹；研究组出现 1 例恶心，均不影响继续治疗。两组不良反应的发生情况比较差异无统计学意义(P>0.05)。

3 讨论

PD 患者伴发认知功能障碍易进展为痴呆，会进一步削弱患者的自理能力，加重家庭和社会负担。近几年，PD 患者的非运动症状越来越受到医学领域的关注，但遗憾的是尚无确定的治疗 PD 伴认知功能障碍的有效药物[19,20]。对于 PD 伴轻度认知功能障碍患者而言，早期诊断和治疗对避免进展为痴呆具有重要意义[21]。

从中医病名中的＂震颤＂、＂健忘＂、＂呆病＂中可见与 PD、认知功能障碍诸多相似的临床症状描述。有医家认为＂震颤＂主要是因肾水匮乏导致肝木无所养，从而引起肝火亢盛而克脾，而脾虚则无法布津液，最终导致津液聚集形成痰，其病因病机不外乎是肾、肝、脾亏虚的缘故[22,23]。肝藏血，肝血可滋养筋膜，肝血充足，筋力方强健，肢体方运动自如，而一旦肝血不沛，筋膜无以濡养，则手足震颤等症即现[24,25]。同时，肾藏精，主骨生髓，脑居颅内为髓之海，主骨生髓通于脑，故而当肾精充盈则能滋养脑髓，脑的生理功能就能维持正常，而一旦肾精匮乏无以滋养脑髓，髓海枯竭，脑无所养，则元神愈发昏聩，严重时发展为痴呆。精血既相互滋生、相互转化，即＂精血同源＂[26]。因此，PD 和认知功能障碍的起病和肝、肾息息相关，病机为＂本虚标实＂，虚＂则是肝肾亏虚，实则是＂风、火、痰、瘀＂变证丛生，蕴塞脑窍，临床上从肝肾论治 PD 比较常见[27]。

补益肝肾汤中以熟地黄和生地黄为君药，熟地黄滋阴、补血，生地黄清热凉血，养阴、生津，合用可补血生津、滋养肾肝、益精填髓。黄芪益气固表、敛汗固脱，白术补脾益胃，合用可益气健脾，强化后天之本。川芎活血行气，威灵仙通经络、祛风湿、消痰涎，全蝎息风止痉，合用可搜风通络，通畅气血。白芍养血柔肝、敛阴收汗，天麻平肝息风、平抑肝阳、止痉通络，荆芥与防风兼息内外风，肉苁蓉温肾补精[28,29]。诸药配伍共奏养血祛风、化痰止痉、固精收涩之效。研究表明滋补肝肾类中药有助于促进脑微循环的改善，大脑皮质生理功能的提高以及机体免疫力的增强[30]。

此外，本研究结果显示：对照组治疗后 UPDRS 评分有所降低但不明显，MMSE 评分有所降低，总有效率较低，提示患者的认知功能障碍有加重的趋势，说明单纯西医治疗以缓解 PD 的临床症状及体征，减缓病情发展为主，对患者的认知功能无改善作用。反之，研究组 UPDRS 评分明显降低，MMSE 评分明显提高，总有效率高于对照组，说明补益肝肾汤辅助西药治疗能显著提高疗效，且能明显改善患者的认知功能。有研究表明中药能通过提高一些纹状体中抗氧化酶 (如 CAT、SOD、GSHPX) 的含量来促进纹状体抗氧化的能力增强以及神经元凋亡指数减小，将来有必要深入地对中药治疗的机理进行探究。

报道显示，中医治疗 PD 具有以下明显的优势：辨证论治，能根据患者的具体表现特点灵活加减，实现多靶点治疗[31]；疗效持续且不良反应一般轻微。虽然目前中药在 PD 的治疗领域不能占据主导地位，但可辅助西药显著增进疗效，并改善患者的非运动症状，副作用相对少，对延缓 PD 的病理进程具有重要意义。

综上所述，补益肝肾汤联合美多巴治疗 PD 患者的临床效果优于美多巴片单药治疗，并可显著改善患者的认知功能障碍，且安全性高，但本研究为单中心、小样本，故治疗的有效性及重复性尚需进一步验证。

参 考 文 献(References)

[1] Kalia L V, Kalia S K, Lang A E. Disease-modifying strategies for Parkinson's disease[J]. Movement Disorders, 2015, 30(11): 1442

[2] Hauser R A, Isaacson S, Lisk J P, et al. Droxidopa for the short-term treatment of symptomatic neurogenic orthostatic hypotension in Parkinson's disease (nOH306B)[J]. Movement Disorders, 2015, 30(5): 646-654

[3] Mak E, Su L, Williams G B, et al. Baseline and longitudinal grey matter changes in newly diagnosed Parkinson's disease: ICICLE-PD study[J]. Brain, 2015, 138(10): 2974-2986

[4] Bella S D, Benoit C, Farrugia N, et al. Effects of musically cued gait training in Parkinson's disease: beyond a motor benefit [J]. Annals of the New York Academy of Sciences,2015, 1337(1): 77-85

[5] Deng H X, Yong S, Yi Y, et al. Identification of TMEM230 mutations in familial Parkinson's disease[J]. Nature Genetics, 2016, 48(7): 733

[6] Walton C C, Shine J M, Mowszowski L, et al. Impaired cognitive control in Parkinson's disease patients with freezing of gait in response to cognitive load [J]. Journal of Neural Transmission, 2015, 122(5): 653-660

[7] Planetta P J, Kurani A S, Shukla P, et al. Distinct functional and macrostructural brain changes in Parkinson's disease and multiple system atrophy[J]. Human Brain Mapping, 2015, 36(3): 1165

[8] Xia XH, Yuan YY, Liu M.The assessment of the chronic hepatotoxicity induced by Polygoni Multiflori Radix in rats: A pilot study by using untargeted metabolomics method[J]. J Ethnopharmacol, 2017, 203: 182-190

[9] Bagga V, Dunnett S B, Fricker R A. The 6-OHDA mouse model of Parkinson's disease-terminal striatal lesions provide a superior measure of neuronal loss and replacement than median forebrain

bundle lesions[J]. Behavioural Brain Research, 2015, 288(24): 107

[10] Concannon R M, Okine B N, Finn D P, et al. Differential upregulation of the cannabinoid CB_2 receptor in neurotoxic and inflammation-driven rat models of Parkinson's disease [J]. Experimental Neurology, 2015, 269: 133-141

[11] Roodveldt C, Bertoncini C W, Andersson A, et al. Chaperone proteostasis in Parkinson's disease [J]. Embo Journal, 2015, 28(23): 3758-3770

[12] Golpich M, Amini E, Hemmati F, et al. Glycogen synthase kinase-3 beta (GSK-3β) signaling: Implications for Parkinson's disease [J]. Pharmacological Research, 2015, 97(12): 16

[13] Paul G, Zachrisson O, Varrone A, et al. Safety and tolerability of intracerebroventricular PDGF-BB in Parkinson's disease patients [J]. Journal of Clinical Investigation,2015, 125(3): 1339-1346

[14] Zhang H, Duan C, Yang H. Defective Autophagy in Parkinson's Disease: Lessons from Genetics [J]. Molecular Neurobiology, 2015, 51(1): 89-104

[15] Valadas J S, Vos M, Verstreken P. Therapeutic strategies in Parkinson's disease: what we have learned from animal models [J]. Annals of the New York Academy of Sciences, 2015, 1338(1): 16

[16] Baram O, Amit T, Kupershmidt L, et al. Neuroprotective and neurorestorative activities of a novel iron chelator-brain selective monoamine oxidase-A/monoamine oxidase-B inhibitor in animal models of Parkinson's disease and aging [J]. Neurobiology of Aging, 2015, 36(3): 1529-1542

[17] Chen Y, Xiong M, Dong Y, et al. Chemical Control of Grafted Human PSC-Derived Neurons in a Mouse Model of Parkinson's Disease[J]. Cell Stem Cell, 2016, 18(6): 817

[18] Ye Z, Altena E, Nombela C, et al. Improving response inhibition in Parkinson's disease with atomoxetine[J]. Biological Psychiatry, 2015, 77(8): 740-748

[19] Yang L, Sun X, Geng X. Effects of psoralen on chondrocyte degeneration in lumbar intervertebral disc of rats[J]. Pakistan Journal of Pharmaceutical Sciences, 2015, 28(2(Suppl)): 667-670

[20] Chen X, Hu C, Dai J, et al. Metabolomics analysis of seminal plasma in infertile males with kidney-yang deficiency: a preliminary study[J]. Evidence -Based Complementary and Alternative Medicine, 2015, 2015(2):1-8

[21] Coyle M, Shergis J L, Liu S, et al. Safety of chinese herbal medicine for chronic obstructive pulmonary disease [J]. Evidence-based Complementary and Alternative Medicine,2015, 20(15) :380678

[22] Zhang L, Zhao X, Wang F, et al. Effects ofMorinda officinalisPolysaccharide on Experimental Varicocele Rats [J]. Evidence-based complementary and alternative medicine : eCAM, 2016, 2016(4): 5365291

[23] Rogdaki M, Jauhar S, Mccutcheon R, et al. Treatment-Resistant Schizophrenia in a Patient With 17q12 Duplication [J]. Biological Psychiatry, 2015, 80(4): e19-e20

[24] Factor S A, Friedman J H, Lannon M C, et al. Clozapine for the treatment of drug induced psychosis in Parkinson's disease: Results of the 12 week open label extension in the PSYCLOPS trial [J]. Movement Disorders, 2015, 16(1): 135-139.

[25] Jiao C, Zhu X, Zhang H, et al. EMP acupoint stimulation conducive to increase the effect of weight reduction through aerobic exercise[J]. International Journal of Clinical & Experimental Medicine, 2015, 8 (7): 11317-11321

[26] Jia Y, Du H, Yao M, et al. Chinese herbal medicine for myelosuppression induced by chemotherapy or radiotherapy: a systematic review of randomized controlled trials [J]. Evidence-based complementary and alternative medicine: eCAM, 2015, 2015 (3): 690976

[27] Laguna A, Schintu N, Nobre A, et al. Dopaminergic control of autophagic-lysosomal function implicates Lmx1b in Parkinson's disease[J]. Nature Neuroscience, 2015, 18(6): 826

[28] Zange L, Noack C, Hahn K, et al. Phosphorylated α-synuclein in skin nerve fibres differentiates Parkinson's disease from multiple system atrophy[J]. Brain, 2015, 138(8): 2310

[29] He N, Ling H, Ding B, et al. Region specific disturbed iron distribution in early idiopathic Parkinson's disease measured by quantitative susceptibility mapping [J]. Human Brain Mapping, 2015, 36(11): 4407-4420

[30] Johnson M E, Bobrovskaya L. An update on the rotenone models of Parkinson's disease: their ability to reproduce the features of clinical disease and model gene-environment interactions[J]. Neurotoxicology, 2015, 46(23): 101

[31] Bell P T, Gilat M, O'Callaghan C, et al. Dopaminergic basis for impairments in functional connectivity across subdivisions of the striatum in Parkinson's disease [J]. Human Brain Mapping, 2015, 36 (4): 1278

[32] Hu X, Song X, Yuan Y, et al. Abnormal functional connectivity of the amygdala is associated with depression in Parkinson's disease[J]. Movement Disorders, 2015, 30(2): 238-244