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多巴胺能药物对早期帕金森病患者睡眠障碍发生的影响*

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摘要 目的:探讨多巴胺能药物及其它因素与早期帕金森病患者睡眠障碍之间的关系。**方法:**选择 84 名早期帕金森病患者作为病例组, 87 名健康人作为对照组。采用帕金森病睡眠量表(PDSS)评价患者的睡眠状况。采用非条件 Logistic 回归分析早期帕金森病患者睡眠障碍的影响因素。**结果:**早期帕金森病组 PDSS 总评分显著低于对照组($P=0.000$); HAMD 评分则显著高于对照组($P=0.000$)。早期帕金森病患者睡眠障碍的主要类型为失眠。使用多巴胺能药物($OR=5.50, 95\%CI: 1.96-15.81$)是早期帕金森病患者发生睡眠障碍的危险因素; 而较低的 HAMD 评分($OR=0.35, 95\%CI: 0.13-0.93$)则显著降低其睡眠障碍风险。**结论:**早期帕金森病患者存在睡眠障碍, 多巴胺能药物和抑郁可能促进和加重其睡眠障碍。

关键词: 帕金森病; 睡眠障碍; 多巴胺能药物; 抑郁

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Effects of Dopaminergic Agents on the Sleep Disorders of Parkinson Disease Patients at Early Stage*

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ABSTRACT Objective: To evaluate the relationship between dopaminergic agents and sleep disorders of Parkinson disease (PD) patients at early stage. **Methods:** Eighty-four consecutive PD patients at early stage (Hoehn-Yahr grade I - II) and age-matched 87 healthy controls were enrolled in this study. Parkinson disease sleep scale (PDSS) was used to evaluate sleep status. Non-conditional Logistic regression models were used to calculate odds ratios and its corresponding 95% confidence interval (95%CI). **Results:** The PDSS score of PD group was significantly lower than that of control group ($P=0.000$), but the score of Hamilton depression rating scale (HAMD) of PD group was significantly higher than that of control group ($P=0.000$). Agrypnia was found the main type of sleep disorder for PD patients at early stage. Dopaminergic agents ($OR=5.50, 95\%CI: 1.96-15.81$) could increase risk of sleep disturbance, and lower score of HAMD ($OR=0.35, 95\%CI: 0.13-0.93$) could decrease risk of sleep disorders among PD patients. **Conclusion:** Different types of sleep disorder could be found in PD patients at early stage. Dopaminergic agents and depression may make the situation of sleep disorders worse for PD patients at early stage. Intervention and treatment measures should be introduced to prevent development of sleep disorders among PD patients at early stage.

Key words: Parkinson disease; Sleep disorders; Dopaminergic agents; Depression

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前言

帕金森病(Parkinson disease, PD)是一种发病率较高的神经系统退行性疾病,常表现为以下两方面的症状:一是运动症状,包括:肌强直、静止性震颤、运动迟缓、姿势不稳等^[1-3];二是非运动症状(non-motor symptoms, NMS),包括:自主神经功能障碍、认知障碍、情绪障碍和睡眠障碍^[4,5]。流行病学资料显示,60-98%的PD患者具有睡眠障碍^[6,7],是PD和其它神经退行性疾病患者的常见症状。PD患者的睡眠障碍具体表现为日间过度嗜睡、入睡延迟、睡眠维持困难、快速眼动睡眠期行为障碍(rapid eye movement sleep behavior disorder, RBD)、不宁腿综合征(restless legs syndrome, RLS)和周期性肢体运动障碍(period-

ic limb movements disorder, PLMD)等^[8-10]。PD患者睡眠障碍的病因学尚不明确,研究提示可能与运动障碍、多巴胺能药物以及情绪障碍有关^[11,12]。本研究拟采取病例对照的研究方法探讨多巴胺能药物及其它可能因素与早期帕金森病患者睡眠障碍的关系。

1 对象与方法

1.1 研究对象

本研究纳入 84 例于 2011 年 6 月—2012 年 12 月期间我院专科门诊就诊和住院治疗,符合英国帕金森病协会(United Kingdom Parkinson Disease Society, UKPDS)诊断标准^[13],且 Hoehn-Yahr 分期为 I ~ II 期(帕金森病早期)的原发性帕金森病患者作为 PD 组。排除继发性帕金森综合征、帕金森叠加综

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合征,痴呆、颅内器质性病变和其他神经系统疾病、精神疾病,以及心脏、肾脏、肺脏、肝脏、内分泌系统等严重疾病患者。此外,另选择 87 例健康人作为对照组。所有研究对象均签署知情同意书。

1.2 资料收集

按照文献^[4]介绍的方法,采用帕金森病睡眠量表(Parkinson disease sleep scale, PDSS) 分别对 PD 组和对照组的睡眠情况进行评分。该量表共包含 15 项帕金森病睡眠障碍的相关问题,主要询问调查对象的夜间总体睡眠质量、入睡困难和睡眠维持困难、PLMD 和 RLS、夜尿、夜间精神状况和运动状况以及过度嗜睡(excessive daytime sleepiness, EDS)等情况。每项问题根据症状严重程度采用 0-10 分的评分制,量表最高总分为 150 分。本研究还采用简易精神状态量表(minimum mental state examination, MMSE)和汉密尔顿抑郁评价量表(Hamilton depression rating scale, HAMD)分别评估两组研究对象现在或过去 4 个月的嗜睡程度、认知状况和抑郁程度。由经培训的神经内科医师采用自制问卷以面对面形式收集研究对象的人口统计学资料、药物治疗、病史等基本资料。

1.3 统计分析

连续性变量资料以均数 $\pm$ 标准差表示,两独立样本均数的比较采用 t 检验;计数资料率的比较采用卡方检验;早期 PD 患者睡眠障碍与多巴胺能药物之间的关系采用一步法非条件 Lo-

gistic 回归分析。数据分析采用 SPSS 16.0 统计软件。假设检验水准设为 0.05,所有统计检验均采用双侧检验,以 $P<0.05$ 认为有统计学意义。

2 结果

2.1 一般情况

PD 组患者的病程范围为 1.6-11 年,平均为 (4.57 ± 1.26) 年。PD 组和对照组的平均年龄分别为 (62.70 ± 2.42) 岁和 (61.83 ± 2.51) 岁,两组年龄无显著差异($P=0.71$)。PD 组和对照组的男性比例分别为 52.38%(44/84)和 52.87%(46/87),两组性别构成无显著差异($P=0.94$)。PD 组 PDSS 平均评分 (109.29 ± 16.94) 显著低于对照组的 (137.34 ± 10.65) ($P=0.000$),HAMD 评分 (9.08 ± 1.66) 显著高于对照组 (2.49 ± 0.49) ($P=0.000$)。PD 组 MMSE 评分 (26.68 ± 2.51) 与对照组 (25.33 ± 2.64) 比较无显著差异($P=0.57$)。具体见表 1。

2.2 早期 PD 患者的 PDSS 评分特征

PD 患者睡眠障碍的主要类型为失眠,其中睡眠维持困难占 39.28%(33/84)、入睡困难占 23.81%(20/84)、早醒占 16.67%(14/84);在导致失眠的原因中,以夜尿症最为常见,约占 54.76%(46/84),其次是逼真梦境(25%, 21/84)。11(13.09%)例患者存在 EDS; 12 例(14.29%)伴有 RLS。具体见表 2。

表 1 早期 PD 患者与健康对照的一般情况比较

Table 1 Characteristics of Parkinson disease patients at early stage compared with controls

Characteristics	PD group(n=84)	Control group(n=87)	P-value
Gender(%)			0.22
Male	64 (76.19)	59 (67.81)	
Female	20 (23.81)	28 (32.19)	
Age (years)	62.70 $\pm$ 2.42	61.83 $\pm$ 2.51	0.71
Scores of PDSS	109.29 $\pm$ 16.94	137.34 $\pm$ 10.65	0.000
Scores of HAMD	9.08 $\pm$ 1.66	2.49 $\pm$ 0.49	0.000
Scores of MMSE	26.68 $\pm$ 2.51	25.33 $\pm$ 2.64	0.57

表 2 早期 PD 患者的 PDSS 评分特征

Table 2 Characteristics of PDSS score of Parkinson disease patients at early stage

Sleep disturbances	No. of patients	Ratio (%)
Insomnia		
Difficulty in staying asleep,	33	39.28
Delay in falling asleep	20	23.81
Early wake	14	16.67
Reasons of insomnia		
Nycturia	46	54.76
Fidelity dream	21	25.00
Tremor	19	22.62
Difficulty turn the body over	15	17.86
Spasm/pain of limbs	6	7.14
EDS	11	13.09
RLS	12	14.29
Mild	8	9.52
Moderate	3	3.57
Severe	1	1.19
PLMD	7	8.33

2.3 早期 PD 患者睡眠障碍与多巴胺能药物治疗的关系

以 PDSS 评分 < 6 分作为症状严重判定标准^[6], PD 组共有 39 例患者发生睡眠障碍。将 PD 组患者按是否发生睡眠障碍作为因变量, 将性别、年龄、病程时长、Hoehn-Yahr 分期、MMSE 评分、HAMD 评分和多巴胺能药物治疗等 7 个变量作为自变量进行多因素非条件 Logistic 回归分析发现: 多巴胺能药物治

疗(OR=5.50, 95%CI: 1.96-15.81)显著提升 PD 患者睡眠障碍发生风险, 而较低的 HAMD 评分(OR=0.35, 95%CI: 0.13-0.93)则显著降低 PD 患者睡眠障碍发生风险; 性别、年龄、Hoehn-Yahr 分期、病程时长和 MMSE 评分等因素与 PD 患者发生睡眠障碍无显著关联($P>0.05$)。具体见表 3。

表 3 早期 PD 患者发生睡眠障碍危险因素的非条件 Logistic 回归分析

Table 3 Risk factors of Sleep disturbances in Parkinson disease patients at early stage analyzed by non-conditional Logistic Regression models

Characteristics	Sleep disturbances		OR	95%CI
	Yes (%)	No (%)		
Gender				
Male	20 (51.28)	24 (53.33)	0.92	0.36-2.38
Female	19 (48.72)	21 (46.67)	Ref	
Age (years)				
≤ 60	18 (46.15)	25 (55.56)	0.69	0.26-1.77
>60	21 (53.85)	20 (44.44)	Ref	
Stage of Hoehn-Yahr				
I	16 (41.03)	26 (57.78)	0.51	0.19-1.32
II	23 (58.97)	19 (42.22)	Ref	
Dopaminergic agents using				
Yes	26 (66.67)	12 (26.66)	5.50	1.96-15.81
No	13 (33.33)	33 (73.34)	Ref	
Scores of HAMD				
≤ 8	17 (43.59)	31 (68.89)	0.35	0.13-0.93
>8	22 (56.41)	14 (31.11)	Ref	
Scores of MMSE				
≤ 25	18 (46.15)	26 (57.78)	0.63	0.24-1.62
>25	21 (53.85)	19 (42.22)	Ref	
Duration of disease (years)				
≤ 5	16 (41.06)	28 (62.22)	0.42	0.16-1.11
>5	23 (58.94)	17 (37.78)	Ref	

3 讨论

研究表明^[15], PD 患者之所以发生睡眠障碍, 首先是由于患者多巴胺能神经元丢失, 进而打破了正常生理状态下的神经递质代谢平衡。这些提示自主神经功能失调导致的运动和精神症状, 以及使用抗帕金森病药物等都有可能影响 PD 患者的睡眠质量。目前, 对早期 PD 患者的睡眠障碍发生状况及其可能的影响因素报道尚少不多见。本研究采用病例对照研究方法探讨了早期 PD 患者自身的宿主因素及多巴胺能药物治疗与其睡眠障碍之间的关系。

本研究采用帕金森病睡眠量表(PDSS)作为早期 PD 患者睡眠障碍的筛查工具, 该量表具有较高信度和灵敏度^[6]。近 3/4 帕金森病患者存在睡眠障碍^[3]。与之相似的是, 本研究发现早期 PD 患者约有 46% 患有睡眠障碍。导致患者失眠最主要的原因是夜间睡眠维持困难, 其它重要原因还包括夜尿症、早醒、REM 行为异常和 RLS^[16]。PD 患者睡眠障碍通常与其生存质量高低

联系紧密^[17]。PD 患者的睡眠障碍形成机制较为复杂, 且受多种因素影响。前期研究认为, 大年龄、夜间运动症状、精神症状(抑郁和幻觉)和治疗药物均可扰乱睡眠结构从而导致运动波动进而形成睡眠障碍^[4,12]。虽然本研究未观察到早期 PD 患者的年龄、性别、疾病严重程度(Hoehn-Yahr 分期)以及病程长短与其发生睡眠障碍存在显著关联, 但是我们发现多巴胺能药物治疗可显著提高早期 PD 患者发生睡眠障碍的风险。一般认为, PD 患者 Hoehn-Yahr 分期越高则左旋多巴治疗的时间越长, 治疗剂量也越高, 患者随治疗时间延长, 患者的睡眠质量会明显降低并可能出现 EDS, 因而多巴胺能药物治疗可能会促进和加重 PD 患者的睡眠障碍。

PD 患者的另一个并发症是抑郁症。有研究发现 PD 患者中有将近一半左右的人患有抑郁, 这部分患者不仅有睡眠障碍而且其精神心理症状表现较为明显。研究提示, PD 患者抑郁的发生可能受病程和病情严重程度影响^[18,19]。本研究结果显示, 早期 PD 患者的抑郁评分显著高于正常人群, 约 56% 的早期 PD

患者 HAMD 抑郁评分高于 8 分以上。此外,本研究还发现 HAMD 抑郁评分与早期 PD 患者发生睡眠障碍的显著负相关,进一步提示,尽早采取有针对性的抑郁干预和治疗措施,将有利于改善 PD 患者的睡眠质量和并提高其生存质量^[2021]。

综上所述,多巴胺能药物治疗可能会促进或者加重早期 PD 患者发生睡眠障碍的风险,与此同时,由 PD 疾病本身导致早期 PD 患者产生的抑郁可能会进一步促进睡眠障碍的发生和发展。综合结果提示,在 PD 疾病早期即采取改善早期 PD 患者睡眠质量的预防和治疗综合措施将有益于提高其生存质量。

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