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快速眼动睡眠期行为障碍(RBD)的帕金森病临床特征分析*

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摘要 目的:探究合并不同发作形式的快速眼动睡眠期行为障碍(RBD)与帕金森病的临床特点及自主神经功能障碍变化。**方法:**采用快速眼动睡眠行为障碍筛查量表及帕金森综合评分量表(Unified Parkinson's disease rating scale),对20例合并简单型(RBD)的帕金森病患者(RBD-简单组)与20例合并复杂型(RBD)的帕金森病患者(RBD-复杂组)进行研究。**结果:**两组帕金森病患者的一般情况、左旋多巴药物日剂量、疾病病程等无统计学差异($P>0.05$)。合并复杂型(RBD)的帕金森病患者运动部分评分高于合并简单型(RBD)的帕金森病患者($P<0.05$)。两组患者之间在非震颤、强直、运动减少症状均存在统计学差异($P<0.05$), (RBD)复杂组评分均高于(RBD)简单组。多因素logistics回归显示,复杂型(RBD)的存在与UPDRS-III部分评分相关,而与年龄、病程、教育年限、左旋多巴药物日剂量等无显著相关,与运动减少症状最为相关,与震颤、非震颤、强直症状无相关性。两组患者运动障碍类型与(RBD)发作形式无明显相关性($P=0.108$)。**结论:**合并复杂型(RBD)的帕金森病患者运动症状更重,并且累及运动障碍的诸多方面。帕金森病患者存在复杂型(RBD)症状主要与UPDRS-III评分相关,其中与运动减少方面显著相关。

关键词:快速眼动睡眠行为障碍;帕金森病;自主神经功能障碍

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Clinical Features of Parkinson's Disease with Behavioral Disorder During Rapid Eye Movement Sleep*

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ABSTRACT Objective: To explore the clinical features and autonomic nerve dysfunction of REM sleep behavior disorder and Parkinson's disease combined with different seizure forms. **Methods:** 20 patients with Parkinson's disease combined with simple RBD (RBD-simple group) and 20 patients with complex RBD-complex group (RBD-complex group) were compared and studied by using the RAPID eye movement sleep behavior disorder screening scale and the Unified Parkinson's Disease Rating Scale. **Results:** There were no significant differences in the general condition, daily dose of levodopa drug, and the course of disease between the two groups ($P>0.05$). The motor scores of Parkinson's disease patients with complex RBD were higher than those of Parkinson's disease patients with simple RBD ($P<0.05$). There were statistical differences in non-tremor, rigidity, and reduced motor symptoms between the two groups ($P<0.05$). The scores of the RBD complex group were higher than those of the RBD simple group. Multivariate logistic regression showed that the existence of complex RBD was related to partial scores of UPDRS-III, but not significantly related to age, course of disease, years of education, daily dose of levodopa drug, etc., and was most related to reduced symptoms of exercise, and was not related to the symptoms of tremor, non tremor and rigidity. There was no significant correlation between the type of movement disorder and the form of RBD in the two groups ($P=0.108$). **Conclusion:** Pd patients with complex RBD have more severe motor symptoms and involve many aspects of motor disorders, which is associated with UPDRS - III score, and is most related to reduced symptoms of exercise.

Key words: RAPID eye movement sleep behavior disorder; Parkinson's disease; Autonomic nervous dysfunction

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前言

帕金森疾病是神经系统变性疾病中的一种,以静止性颤动、运动缓慢、姿势步态障碍、躯体肌僵直等运动症状作为特征

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性表现,同时也存在自主神经功能障碍、睡眠障碍等非运动症状^[1,2]。当前,已有大量临床研究指出,合并和未合并 RBD 症状的帕金森病患者存在明显不同的临床特征,患者年龄高,疾病病程进展速度快,发病病程长,运动症状重,认知障碍明显^[3,4]。但关于帕金森病患者中,并伴随着不同发作类型 RBD 症状,这些患者之间的临床表现的差异性少有报道,本文将研究合并不同发作形式的 RBD 与帕金森病运动症状之间的关联。

1 资料与方法快速眼球运动睡眠期行为障碍(RBD)

1.1 一般资料

选取 2019 年 1 月至 2020 年 12 月,就诊于我院神经内科,遵照帕金森病临床诊断标准,诊断为帕金森病的患者。在帕金森病患者中,采用 RBDSQ 筛选有 RBD 症状的患者,所选择的人组患者为 RBDSQ 总分 26 分者。为了进一步提高对 RBD 症状诊断的准确性,还需要问家人,关于患者的睡眠基本情况,睡眠期间是否存在大声喊叫、做噩梦,出现异常状况,如不自主肢体活动等。

1.2 排除标准

除外继发性帕金森病(感染、药物、毒物等引起)、帕金森叠加综合征、有关疾病和既往精神病史,除外药物、酒精滥用,除外其余神经系统疾病如癫痫、重度认知功能障碍患者。

1.3 方法

征得入组人员许可,进行相关资料收集,完成 RBD 问卷量表筛查,见表 1。依据 RBDSQ 第六项目的得分,将 RBD 发作形式分为简单型、复杂型组。所有资料的收集采用问卷调查方式,由受试者及其家属共同参与。帕金森病患者运动状评估依据 UPDRS-III 所得评分,并收集所有受试者帕金森病病程、左旋多巴药物日剂量(mg/d)、年龄、性别等基本资料。

1.4 分析方法

表 1 两组患者的一般情况,年龄、教育年限、用药剂量、病程、UPDRS-III 评分比较

Table 1 Comparison of general situation, education, drug dosage, course of the disease, UPDRS score - III between two groups

Groups	n	Male/female	Age	Years of Education (year)	doses (mg/d)	Course of Disease (year)	UPDRS-III Total score
RBD simple	33	15/18	62.89± 8.82	9.79± 2.85	446.99± 412.55	4.30± 3.34	23.85± 14.44
RBD complex	42	26/16	66.32± 7.23	10.25± 2.92	589.76± 419.45	5.61± 3.63	31.80± 15.11
P value			0.076	0.494	0.143	0.111	0.023

表 2 两组患者运动症状比较

Table 2 Comparison of exercise symptoms between two groups

	n	tremor	Non-tremor	stiffness	Sports to reduce
RBD simple	33	2.92± 2.45	11.71± 7.75	4.27± 4.37	6.29± 3.71
RBD complex	42	4.54± 4.57	16.04± 7.89	6.51± 4.99	8.33± 3.30
T value		-1.858	-2.38	-2.068	-2.494
P value		0.072	0.02	0.042	0.015

Note: According to the grouping method reported in the literature, the tremor correlation is the total score of the 20th and 21st items in the UPDRS-III score, the non-tremor correlation is the total score of the 18th, 19, 22, 27-31 items, and the tonic correlation is the total score The total score of 22 items, sports reduction related to the 18th, 19, 27-29, 31 total score.

本文利用 SPSS19.0 软件,分析所得数据,以平均数± 标准差($\bar{x} \pm s$)的形式,表示计量数据资料,对比两独立样本资料的均值,应用 t 检验方法进行。以率(%)的形式,表示计数资料,应用卡方检验,并用 logistics 回归(逐步向前法)探究多变量之间的相关性, $P < 0.05$ 认为差异具备统计学意义。

2 结果

两组患者间年龄、教育年限、左旋多巴药物日剂量情况比较(表 1):年龄 RBD 简单组为 62.89 ± 8.82 岁,RBD 复杂组为 66.32 ± 7.23 岁,两组之间无统计学差别($P = 0.076$)。就教育年限而言,RBD 简单组为 (9.79 ± 2.85) 年,RBD 复杂组为 (10.25 ± 2.92) 年,无统计学差异($P = 0.494$)。左旋多巴药物日剂量情况 RBD 简单组为 (446.99 ± 412.55) mg/d,RBD 复杂组为 (589.76 ± 419.45) mg/d,RBD 复杂组平均值稍高于 RBD 简单组,但无明显统计学差异($P = 0.143$)。RBD 简单组平均病程 (4.30 ± 3.34) 年,RBD 复杂组平均病程 (5.61 ± 3.63) 年,两组之间病程无统计学差异($P = 0.111$)。

两组患者间 UPDRS-III 评分比较(表 2):RBD 简单组为 (23.85 ± 14.44) 分,RBD 复杂组为 (31.80 ± 15.11) 分,两组之间 UPDRS-III 评分比较,具有统计学差异($P = 0.023$)。进一步分析(表 3)显示,两组之间非震颤、强直、运动减少症状均存在统计学差异,RBD 复杂组评分均高于 RBD 简单组。经多因素 logistics 回归(表 4、表 5)显示,RBD 类型只与 UPDRS-III 部分评分相关,与年龄、病程、教育年限、左旋多巴药物日剂量等无显著相关,细化来看,与运动减少最为相关,与震颤、非震颤、强直无相关。

两组患者间应用卡方检验(表 6)看出,两组患者运动障碍类型与 RBD 发作形式无明显相关性($\chi^2 = 2.616, P = 0.108$)。

3 讨论

帕金森病的临床症状主要分为典型运动症状及多种多样

的非运动症状。非运动症状涉及机体多个系统,出现多样症状,如循环系统、消化系统、生殖泌尿系统、觉醒-睡眠系统等功能障碍^[9]。帕金森病患者睡眠障碍患病率高,研究显示,睡眠相关性伤害的发生率,在合并 RBD 及未合并 RBD 症状的患者中为 33%和 6%^[6]。由于 RBD 导致睡眠质量受损及睡眠相关伤害的高发性,临床上应积极治疗 RBD^[7,8]。

表 3 复杂 RBD 相关因素的 Logistic 回归分析
Table 3 Logistic regression analysis results of relevant factors in presence of complex RBD

Project	Regression coefficients	RBD complex		
		OR value	95% confidence interval	P
UPDRS-III Total score	0.038	1.038	1.004-1.075	0.028
Age	-	-	-	-
Education years	-	-	-	-
Daily dose of levodopa drug	-	-	-	-
Course of disease	-	-	-	-
Constant	-0.808	-	-	0.123

表 4 复杂 RBD 中相关运动症状因素的 Logistic 回归分析结果
Table 4 Logistic regression analysis results of related motor symptom factors in complex RBD

Project	Regression coefficients	OR value	95% confidence interval	P
Tremor	-	-	-	-
Non-tremor	-	-	-	-
Stiffness	-	-	-	-
Sports to reduce	0.177	1.194	1.028-1.387	0.02
Constant	-1.042	-	-	0.078

表 5 运动障碍类型与 RBD 发作形式%2 分析统计表
Table 5 Types of dyskinesias and RBD attacks %2 analysis statistics table

Groups	Tremor	Non-tremor	Total
RBD simple			
RBD complex			
Total			
$\chi^2=2.616$			$P=0.108$

Note: According to the grouping method in the literature, the ratio of the tremor-related sum divided by 7 and the non-tremor-related sum divided by 12 is the type. If the ratio is 22, it is tremor type, and the rest is non-tremor type.

大量报道认为,男性患者多见 RBD,多表现为各种睡眠期间不随意运动,如咀嚼吞咽、喊叫、哭笑、翻滚、跌落、打翻物品等,可能伤及自身或家人,醒来后有时可回忆具体内容^[9,10]。男性患者多为暴力梦境,而女性患者多与生活琐事相关,临床表现相对较安静,因此有时难以发现^[11,12]。本研究共收集患者 40 例,其中男性患者 22 例,女性 18 例,男女患者病例差距不大,与采集资料时对全部患者及其同眠者联合进行 RBD 问卷量表筛查,提高了问卷的灵敏度有关,也有文献报道,RBD 的发病率在男女患者中并无差异,导致女性患者数量少可能因为女性患者症状难以察觉或不愿就医。本研究中复杂型 RBD 患者男性患者为 26 例占复杂型 62%,也反映男性患者 RBD 症状普遍较重。

研究表明,合并 RBD 的帕金森病患者平均应用药物剂量增大可能与此类患者病程较长,运动症状逐渐加重有关^[13]。本

文研究显示,平均左旋多巴药物日剂量组间无明显统计学差异,但两组药物应用剂量大。临床研究发现,抗帕金森药物在治疗疾病的同时,也会引发相关睡眠障碍,导致 RBD 症状的出现。由于本研究样本量较小,尚不能排除左旋多巴药物剂量与 RBD 发作类型间的关系。报道也指出,对出现 RBD 症状的 PD 患者,早期对药物治疗反应良好,如果能够给予早期的干预或治疗,可能会延缓疾病进展,改善预后^[14]。

研究人员推测,在黑质-纹状体以外的多巴胺能神经元变性,致使 RBD 的出现,与无 RBD 症状的 PD 患者相比,合并 RBD 症状,意味着病变范围更大^[15,16]。本研究中严重型患者运动症状更严重。经过进一步分析可以看出,合并复杂型 RBD 症状的 PD 患者,其运动症状已经涉及到多方面的运动功能:如运动减少,僵硬,肢体灵活性等方面。此结果可能与复杂型 RBD 患者存在更为广泛的受损范围有关,同时结合 RBD 的相

关临床表现,也提示着病损范围除了脑干 REM 睡眠期开-关结构,尤其网状大细胞核和蓝斑下区-蓝斑复合体外,其大脑皮质区域等结构也有受损,如 Wen-Ting W 等^[17]研究认为伴 RBD 的 PD 通常伴有额叶功能障碍,由于额叶前部功能失调,在睡眠期间,边缘系统占据优势,出现了更多有关暴力的梦境。经多因素 logistics 回归分析显示,复杂型 RBD 的存在与 UPDRS-III 部分评分显著相关,这种相关性主要体现在运动减少方面。因此,我们推测出复杂型 RBD 患者更为广泛的受损区域主要是控制肢体运动灵活性、协调性、幅度等区域的结构,在复杂型 RBD 患者的红核、黑质等结构中,存在更明显的多巴胺能神经元脱失,其脑内各类神经递质失衡更为严重^[18]。RBD 的存在是帕金森病运动功能变化,尤其是运动迟缓方面的危险因素,并且存在 RBD 症状的帕金森病患者,随着疾病不断进展,其脑干运动中枢进行性病变,RBD 出现频率减少,异常活动减少^[19]。

Folle A D 等^[20]报道指出,以震颤为主要表现的 PD 及以非震颤为主要表现 PD 的患者,会产生 RBD 的概率分别为 14% 和 53%。本文研究结果显示在 75 例患者中,以非震颤型为主的患者为 73 例,约占 97%,而以震颤型为主的患者仅 2 例,不足 3%。结果与以往研究相符^[21]。在伴有复杂型 RBD 的 PD 患者中,非震颤为主的患者为 20 例,占 58%,提示伴复杂型 RBD 症状的 PD 患者,可能多数为非震颤型^[22]。鉴于本研究患者中绝大部分为非震颤型,说明 PD 的病损结构,主要是引发非震颤症状的结构,存在与 RBD 症状相重叠的病损部位^[23]。因此,深入研究 RBD 症状的病理生理机制,尤其是复杂型 RBD 症状的病变过程,将会为 PD 的病变机制研究带来新思路^[24]。

长期观察研究表明,RBD 作为预测神经变性疾病早期生物学标志物,对神经退行性疾病潜伏期的预防和治疗方面具有重要意义^[25,26]。Bugalho P 等^[27]研究表明,针对未给予治疗的帕金森病患者,出现 RBD 最初症状后到出现明显帕金森症状的时间窗很短。本文研究结果表明,复杂型 RBD 的 PD 患者运动症状更重,而在临床工作中,复杂型表现的 RBD 症状更易于发现,因此,我们可以扩大筛查和宣传范围,采用灵敏度高的问卷,必要时给予整夜多导睡眠检测记录仪检测,及早发现此类患者,积极给予长期随访或适宜的治疗措施。因此,RBD 为神经变性疾病临床前期诊断与治疗提供重要依据,因此临床上要高度重视并密切观察 RBD 症状的早期发现,以便及时采取治疗措施。

综上所述,合并复杂型 RBD 的帕金森病患者其运动症状更重,并且容易累及运动障碍的诸多方面。帕金森病患者存在复杂型 RBD 症状主要与 UPDRS-III 评分相关,其中与运动减少方面显著相关。

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