·论著 临床诊治·

初诊帕金森病患者的偏侧化研究

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【摘要】 **目的** 研究初诊未服药帕金森病患者临床偏侧化特征及相关影响因素。**方法** 收集2017-11—2019-09就诊南京医科大学附属脑科医院神经内科门诊的178例初诊未服药帕金森病患者,采用统一帕金森病评定量表(UPDRS)、非运动症状问卷筛查表(NMS Quest)、蒙特利尔认知量表(MoCA)、简易智能状态评估量表(MMSE)、汉密尔顿抑郁量表(HAMD)、汉密尔顿焦虑量表(HAMA)、帕金森病睡眠量表(PDSS)对受试者进行评估,根据UPDRS第三部分(UPDRS-Ⅲ)及病史分为优势侧起病组(DS-PD)及非优势侧起病组(NDS-PD),比较2组临床资料。**结果** NDS-PD组UPDRS-Ⅲ评分、H-Y分期高于DS-PD组,2组比较差异均有统计学意义($P<0.05$)。多因素二元Logistic回归分析示,女性(*OR*=2.27,95% *CI* 1.145~4.524)及NMS Quest评分高(*OR*=1.189,95% *CI* 1.058~1.337)是PD患者非优势侧起病的危险因素。**结论** 性别可能是帕金森病患者偏侧起病的影响因素,非优势半球起病的PD患者运动及非运动症状受累更严重。在疾病早期,应更注重非优势侧起病的PD患者,并制定规范的个体化治疗方案。

【关键词】 初诊帕金森病;偏侧化;运动亚型;运动症状;非运动症状
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Study on lateralization of newly diagnosed patients with Parkinson's disease

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【**Abstract**】 **Objective** To analyze the clinical lateralization characteristics and related influencing factors in patients with newly diagnosed Parkinson's disease without medication. **Methods** A total of 178 patients with newly diagnosed Parkinson's disease who did not take medication were enrolled in the Department of Neurology, Affiliated Brain Hospital of Nanjing Medical University from November 2017 to September 2019. The unified Parkinson's disease rating scale (UPDRS), non-motor symptom questionnaire (NMS Quest), Montreal cognitive scale (MOCA), Hamilton depression scale (HAMD), Hamilton anxiety scale (HAMA), Parkinson's disease sleep scale (PDSS) was used to evaluate subjects, and they were divided into right-onset group and left-onset group according to UPDRS part III (UPDRS-Ⅲ) and medical history. Clinical data between the two groups were compared ($P<0.05$). **Results** The UPDRS-Ⅲ score and H-Y stage were higher in NDS-PD group than DS-PD group; Binary Logistic regression analysis showed that female (*OR*=2.27, 95% *CI* 1.145-4.524) and higher NMS Quest score (*OR*=1.189, 95% *CI* 1.058-1.337) were the risk factors for non-dominant side onset in patients with PD. **Conclusion** Gender may be an influential factor in lateral onset of PD patients. PD patients with non-dominant hemisphere onset are more seriously affected by motor and non-motor symptoms. In the early stage of the disease, more attention should be paid to PD patients with non-dominant hemisphere onset and standardized individualized treatment plans should be formulated

【**Key words**】 Newly diagnosed Parkinson's disease; Lateralization; Motor subtype; Motor symptoms; Non-motor symptoms

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帕金森病(Parkinson's disease,PD)是全球第二大神经退行性病变,主要表现为运动迟缓、震颤、僵直等运动症状以及嗅觉减退、便秘、睡眠障碍等非运动症状[1-2]。偏侧或不对称起病是PD显著的临床特征[3],脑影像及神经病理的相关研究也证实PD的不对称性[4]。2015年国际运动障碍协会(Movement Disorder Society,MDS)提出运动症状起病的偏侧化是帕金森病诊断的支持证据,而对称起病归为诊断帕金森病的"警示征"[5]。有研究表明,PD患者的非运动症状与运动症状偏侧起病存在相关性,但目前研究较少[6-7]。本研究以初诊未服药的PD患者为研究对象,探讨偏侧起病PD患者间的运动、非运动症状的差异及相关影响因素。

1 对象与方法

1.1 研究对象 收集2017-11—2019-09南京医科大学附属脑科医院神经内科门诊就诊的178例初诊未服药的帕金森病患者,其中男88例,女90例,均为右利手,所有受试者均由2名以上神经专科医生体格检查,本研究患者均知情同意,并签署知情同意书。

1.1.1 初诊PD入组标准:(1)诊断符合2015年MDS提出的PD诊断标准[5];(2)首次就诊,未服用抗帕金森病药物。

1.1.2 初诊PD排除标准:(1)药物、脑血管病、中枢神经系统感染等引起的帕金森综合征或帕金森叠加综合征;(2)已服药的PD患者;(3)不能配合量表评估;(4)合并严重的心、肝、肾等慢性疾病。

1.2 研究方法

1.2.1 收集临床资料:收集患者的性别、年龄、发病年龄及病程等一般资料。采用统一帕金森评估量表(unified Parkinson's disease rating scale,UPDRS)评估患者运动症状,非运动症状问卷筛查表(non-motor symptoms questionnaire,NMS Quest)评估患者非运动症状;简易智能评估量表(mini-mental state examination,MMSE)和蒙特利尔认知评估量表(Montreal cognitive assessment,MoCA)评估患者认知功能;汉密尔顿抑郁量表(Hamilton depression rating scale,HAMD)和汉密尔顿焦虑量表(Hamilton anxiety rating scale,HAMA)评估患者情绪状态,帕金森病患者睡眠量表(Parkinson's disease sleep scale,PDSS)评估患者睡眠情况。

1.2.2 初诊PD患者偏侧化分组:追溯病史,并将UPDRS III的第20~26项的右侧震颤、僵直、运动迟缓总分减去左侧总分,差值>0定义为右侧起病(right-onset Parkinson's disease,R-PD),差值<0定义为左侧起病(left-onset Parkinson's disease,L-PD),排除差值等于0或自述双侧同时起病的患者;此外,本研究招募的均为右利手,故R-PD也为优势侧起病(dominant side,DS-PD),L-PR也为非优势侧起病(non-dominant side,NDS-PD),最终纳入169例初诊PD患者。

1.2.3 亚型分型:根据UPDRS-Ⅱ和Ⅲ计算平均震颤评分和姿势步态异常评分,震颤评分项包括UPDRS-Ⅱ第16项及UPDRS-Ⅲ第20~21项,姿势步态异常评分包括UPDRS-Ⅱ第13~15项及UPDRS-Ⅲ第29~30项。震颤评分均值与姿势步态异常评分均值的比值>1.5,定义为震颤为主型(tremor dominant,TD);均值比值<1.0,定义为姿势不稳/步态障碍型(postural instability/gait difficulty,PIGD),均值比值介于1.0~1.5,定义为不确定型(indeterminate)[8]。

1.3 统计学方法 应用SPSS 26.0统计软件进行统计学分析,符合正态分布的计量资料用均数±标准差($\bar{x}\pm s$)表示,两样本间的比较采用独立样本t检验;非正态分布的计量资料用中位数(四分位数间距)[M(P_{25},P_{75})]表示,两样本间的比较采用Mann-Whitney U检验;计数资料比较采用卡方检验;采用二元Logistic回归进行PD患者偏侧起病影响因素分析,$P<0.05$为差异有统计学意义。

2 结果

2.1 2组人口学资料及运动症状比较 最终纳入的169例初诊PD患者,男82例,女87例;DS-PD组86例,年龄(59.74±7.81)岁;NDS-PD组83例,年龄(61.04±11.44)岁;NDS-PD组UPDRS-Ⅲ评分、H-Y分期高于DS-PD组,2组比较差异均有统计学意义($P<0.05$),2组间性别、年龄、发病年龄、病程、亚型占比差异均无统计学意义($P>0.05$),见表1。

2.2 2组患者非运动症状比较 NDS-PD组NMS Quest总分高于DS-PD组,2组比较差异有统计学意义($P<0.05$),2组MMSE、MoCA、HAMA、HAMD、PDSS总分比较差异均无统计学意义($P>0.05$),见表2。

2.3 影响偏侧起病的相关因素 将是否优势侧起病为因变量,将起病年龄、性别、教育程度、MoCA、HAMD、HAMA、PDSS、NMS Quest评分为协变量进行多因素二元Logistic回归分析,结果显示,女性(OR=2.27,95% CI 1.145~4.524)及NMS Quest评分高(OR=1.189,95% CI 1.058~1.337)是PD患者非优势侧起病的危险因素。见表3。

表1 2组患者社会人口学资料及运动症状比较

Table 1 Comparison of demographic analysis and motor symptoms between two groups

资料	DS-PD(n=86)	NDS-PD(n=83)	$Z/t/\chi^2$值	P值
性别[n(%)]			0.28	0.595
男	40(46.51)	42(50.60)		
女	46(53.49)	41(49.40)		
年龄/(岁,$\bar{x}\pm s$)	59.74±7.81	61.04±11.44	−0.86	0.391
起病年龄/(岁,$\bar{x}\pm s$)	57.65±8.07	57.99±11.50	−0.22	0.394
教育年限/[a,$M(P_{25},P_{75})$]	9(6,12)	9(6,12)	−1.15	0.251
病程/[a,$M(P_{25},P_{75})$]	2(1,3)	2(1,4)	−1.60	0.109
改良H-Y分期	1.5(1,2)	1.5(1,2)	−2.96	0.003
UPDRS-Ⅲ/[分,$M(P_{25},P_{75})$]	19(13,25)	25(18,34)	−3.65	<0.001
TD[n(%)]	30(34.88)	21(25.30)	2.87	0.238
PIGD[n(%)]	46(53.49)	55(66.27)		

注:性别和亚型的比较采用χ^2检验,年龄和起病年龄的比较采用两独立样本的t检验,其余指标的比较采用Mann-Whitney U检验

表2 DS-PD组与NDS-PD组非运动症状比较 [分,$M(P_{25},P_{75})$]

Table 2 Comparison of non-motor symptoms between two groups [scores,$M(P_{25},P_{75})$]

量表	DS-PD (n=86)	NDS-PD (n=83)	Z值	P值
MMSE评分	28(27,29)	28(26,29)	−0.706	0.480
MoCA评分	24(20,27)	24(21,26)	−0.941	0.347
HAMD评分	8(5,13)	9(5,13)	−0.600	0.548
HAMA评分	6(3,10)	7(4,10)	−1.066	0.287
NMS Quest评分	8(5,11)	9(6,12)	−2.140	0.032
PDSS评分	132(112,140)	130(111,142)	−0.090	0.929

表3 偏侧起病相关因素的二元Logistic回归分析

Table 3 Binary Logistic regression analysis of factors related to laterality onset

变量	B	Wald	OR (95% CI)	P值
起病年龄	0.002	0.020	1.002(0.970 ~ 1.036)	0.889
性别(女性)	0.822	5.506	2.27(1.145 ~ 4.524)	0.019
教育年限	−0.069	2.375	0.933(0.855 ~ 1.019)	0.123
MoCA评分	0.009	0.059	1.009(0.937 ~ 1.087)	0.808
HAMD评分	−0.010	0.057	0.990(0.915 ~ 0.915)	0.811
HAMA评分	−0.016	0.086	0.984(0.886 ~ 1.094)	0.769
PDSS评分	0.006	0.351	1.006(0.987 ~ 1.025)	0.554
NMS Quest评分	0.173	8.394	1.189(1.058 ~ 1.337)	0.004

3 讨论

偏侧化起病是帕金森病的显著临床特征,但目前对偏侧化的定义尚不明确[9]。既往对帕金森偏侧化的研究主要以非初诊PD患者为研究对象,探讨偏侧化起病的临床、影像学等特征及影响因素,考虑到药物对PD患者运动、非运动症状的影响[10],故本研究以初诊未服药的PD患者为研究对象,避免药物对临床资料的干扰。本研究显示,DS-PD组与NDS-PD组的人口学资料,如年龄、起病年龄、教育程度、病程、性别等差异均无统计学意义。

PD患者运动症状的偏侧化提示黑质-多巴胺能神经元的不对称丢失[11],优势侧或非优势起病与疾病的严重程度、进展是否相关目前还存在争议。HAM等[9]研究发现,优势侧较非优势侧起病的PD患者运动症状更轻微,此外,CUBO等[7]对652例PD患者进行的运动偏侧化对临床表现与生活质量影响的多中心研究发现,非优势侧起病的PD患者也表现出更严重的运动障碍。本研究中NDS-PD患者运动缺陷更为严重,此结果与上述研究一致,可能机制如下:(1)优势半球基底节区的多巴胺能活性更高,随着多巴能神经元退行性病变,具有更强的代偿能力[12];(2)优势半球M1区神经纤维网络更为丰富,且仅在非优势半球观察到运动相关皮质变薄的现象[13-15];(3)躯体的活动能够增强突触可塑性及神经发生,并减少神经炎症反应,从而改善运动症状[16-17];(4)非优势侧起病患者可能更迟意识到其非惯用手的运动缺陷,导致延迟诊断和症状表现更为严重。在相等程度神经退行性病变中,优势侧起病的PD患者具有更强的调节能力及适应性,运动障碍表现得更为轻微。

PD患者非运动症状是否存在偏侧化表现,目前仍存在争议。本研究对2组非运动症状比较中,除NDS-PD组NMS Quest评分较高外,其余项如MoCA、HAMA、HAMD、PDSS评分等差异均无统计学意义,提示认知、焦虑、抑郁等非运动症状与偏侧化起病无明显相关性,但NDS-PD组NMS Quest评分更高,反

映优势侧起病组患者非运动症状受累更为明显，与ESTHER等[7,18]的研究结果一致，且与上述运动症状偏侧化结果一致，提示优势侧起病的PD患者非运动症状也具有更强的代偿、适应能力。

既往研究报道，环境、遗传、起病年龄、运动等可能是PD患者偏侧化起病的影响因素[19]，但目前尚存在争议。本研究中二元Logistic回归分析显示，性别及NMS Quest评分可能是PD患者偏侧化起病的影响因素，起病年龄无显著影响。国内外关于性别是否影响PD患者偏侧起病的研究较少，目前尚无定论，UITTI等[20]未发现性别与偏侧起病存在相关性，但BENTIVOGLIO等[21]研究发现，左侧起病的PD患者男性多见，性别可能是PD患者偏侧化起病的影响因素，然而此结果未进行矫正，且可能存在入组偏倚，因此，性别是否影响PD起病的偏侧化，还需多中心、多种族并结合影像、遗传等因素进行综合分析。此外，非运动症状，如嗅觉减退[22-42]、便秘、抑郁等[43-52]常出现在运动症状前。本研究显示，NMS Quest评分为运动症状非优势侧起病的危险因素，且在相关分析中，NDS-PD组NMS Quest评分显著高于DS-PD组，仍可能提示优势大脑半球存在的神经代偿、适应机制。

本研究存在以下不足：(1)本研究为单中心、横断面研究；(2)缺乏神经影像学、生物标志物等资料对偏侧化起病差异性及影响因素的综合分析。性别可能是PD患者偏侧化起病的影响因素，非优势半球起病的PD患者运动及非运动症状受累更严重，因此，对非优势侧起病的PD患者，在疾病早期需更注重制定规范的个体化治疗方案。

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