·临床研究·

节律性听觉刺激对帕金森病患者步态的影响

宋金辉 卢祖能

【摘 要】 **目的** 探讨节律性听觉刺激对帕金森病(PD)患者步态的影响。**方法** 选取 PD 患者 42 例,按随机数字法分为对照组(21 例)和听觉刺激组(21 例),2 组均采用常规抗 PD 药物进行治疗,听觉刺激组在此基础上增加节律性听觉刺激训练,要求患者行走时按照节拍进行行走训练,连续训练 3 周。2 组患者均于训练前和训练 3 周后采用美国 Motion Analysis 公司研发的三维运动分析系统进行步态测试,并进行 PD 综合评分量表(UPDRS)第Ⅱ部分和第Ⅲ部分评分、Berg 平衡量表评分(BBS)和 6 min 步行测试(6MWD)。**结果** 治疗 3 周后,听觉刺激组步长和步频分别为(49.5 ± 3.4)cm 和(88.7 ± 8.1)步/min,与组内治疗前和对照组治疗后比较,差异均有统计学意义($P<0.05$)。治疗 3 周后,听觉刺激组的 UPDRS Ⅱ评分、UPDRS Ⅲ评分、6MWD 及 BBS 评分与组内治疗前和对照组治疗后比较,差异均有统计学意义($P<0.05$)。**结论** 节律性听觉刺激训练可辅助改善 PD 患者的步态,促进 PD 患者的运动功能的恢复。

【关键词】 节律性听觉刺激; 帕金森病

The effect of rhythmic auditory stimulation on the gait of Parkinson's disease patients *Song Jinhui, Lu Zhuneng. Department of Neurology, Renmen Hospital of Wuhan University, Wuhan 430060, China*
Corresponding author: Lu Zhuneng, Email: lzn196480@126.com

【**Abstract**】 **Objective** To investigate the effect of rhythmic auditory stimulation on the gait of patients with Parkinson's disease. **Methods** Forty-two patients with Parkinson's disease were divided into an auditory stimulation group and a control group with 21 cases in each. Both groups received conventional drug treatment, but the auditory stimulation group also received rhythmic auditory stimulation training for 10 minutes, 3 times daily for 3 weeks. This involved their attempting to walk in time with a beat. The 2 groups were assessed with gait tests using a 3-dimensional motion analysis system before training and after the 3 weeks of training. Assessments using the united Parkinson's disease rating scale (UPDRS), Berg's balance scale and the 6-minute walk test were carried out. **Results** The auditory stimulation group's average stride length and stride frequency improved significantly after 3 weeks of treatment, and were then significantly better than the control group averages. **Conclusion** Rhythmic auditory stimulation helps improve the gait of Parkinson's disease sufferers and promotes the recovery of motor function.

【**Key words**】 Rhythmic auditory stimulation; Parkinson's disease

姿势步态异常是帕金森病(Parkinson's disease, PD)特征性临床表现之一,是导致 PD 患者运动功能障碍的主要因素之一。PD 患者姿势和步态的异常,部分表现为步幅逐渐变小、步频变慢;部分呈慌张步态,表现为步幅极小,步频变快,且不能及时止步;严重者,行走时全身僵住呈冻结步态(freezing of gait)[1-2]。目前,药物及脑深部电刺激治疗均不能较好地解决 PD 患者姿势步态异常的问题[3],而国内亦鲜见节律性听觉刺激对 PD 患者步态影响的研究报道。本研究采用节拍器释放的节律性声音对 PD 患者行节律性听觉刺激,旨在观察其对 PD 患者步态的影响。

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作者单位:430060 武汉,武汉大学人民医院神经内科
通信作者:卢祖能,Email:lzn196480@126.com

资料与方法

一、研究对象

纳入标准:①根据英国皇后广场脑库(the Queen Square Brain Bank)标准[4]临床诊断为 PD,并与欧洲 2013 年的最新标准[5]进行比对;②简易精神状况量表(mini-mental state examination, MMSE)确定无认知功能障碍,能配合本研究;③常规服用抗 PD 药物后,运动功能能配合本研究。

排除标准:①存在影响步态的神经系统其它疾病;②合并心、肺和骨、关节系统疾病;③合并听力障碍。

选取 2011 年 1 月至 2013 年 3 月在我院神经内科住院且符合上述标准的 PD 患者 42 例,按随机数字表法分为对照组和听觉刺激组,每组 21 例。2 组患者的性别、年龄、病程、MMSE 评分等一般资料比较,差异无

统计学意义($P>0.05$),具有可比性,详见表 1。本研究经医院伦理委员会审核通过,所有受试者均签署知情同意书。

表 1　2 组受试者一般资料

组别	例数	性别(例)		年龄	病程	MMSE 评分
		男	女	(岁,$\bar{x}\pm s$)	(年,$\bar{x}\pm s$)	(分,$\bar{x}\pm s$)
对照组	21	12	9	66.1±7.9	6.7±3.1	28.4±1.7
听觉刺激组	21	11	10	65.7±8.1	6.9±2.9	28.5±1.9

二、训练方法

2 组均采用常规抗 PD 药物治疗(美多巴片、吡贝地尔缓释片、恩他卡朋片等)进行治疗[6]。

听觉刺激组在常规药物治疗的基础上给予节律性听觉刺激:第 1 次开始治疗时,先根据患者日常的行走速度确定患者行走的基础速度,使用节拍软件(beat box software)根据患者行走的基础速度快慢,发出与步行基础速度一致的节拍作为听觉刺激信号,要求患者行走时踩着节拍软件的节拍,按照此节拍进行行走训练。治疗后,再次测量患者的行走速度,作为下次治疗的基础速度[7]。每日训练 3 次,每次 10 min,间歇3 min后进行下一次训练。训练 3 周为 1 个疗程。

三、步态测试

2 组受试者均于训练前及训练 3 周后采用美国 Motion Analysis 公司研发的三维运动分析系统进行步态测试。该系统包括:①硬件——红外数码摄像机、Eagle 工作站及视频处理器、体表定位标记(包括红外反光标志点)和 2 块测力台等;②软件——运动图像采集软件 EvaRT 4.2 版和数据处理软件 Orthotrack 6.2 版。

测量前准备:保持测试环境安静;为避免室外光源干扰,关闭测试空间窗帘;标定步态分析系统并对系统进行校正;充分暴露研究对象躯干及四肢,以保证关节标志点能充分暴露;测试前嘱患者在步道中进行适应性行走。

步态数据采集:测试对象别在头部前额、头顶、枕骨、双侧肩峰、右侧肩胛骨下端、双侧尺骨鹰嘴、双侧腕关节正中、双侧髂前上棘、双侧大腿前中部、双侧股骨外上髁、双侧股骨内上髁、双侧小腿前中部、双侧足外踝、双侧足内踝、双侧足跟共 26 个位点贴体表标记。患者站在力台中央至少 5 s,得到静止站立时各参数值。去掉双侧股骨内上髁、双侧足内踝体表标记,在步行道上行走,要求尽量直线匀速行走,左右腿各记录 3 次,选择视频采集到 2 个以上完整步行周期和最接近平日步行的步态做最终数据分析[8]。

运用三维运动分析系统自带 EvaRT 4.2 版图像采集软件进行数据采集,同时通过自带的 Orthotrack 6.2 版步态分析软件自动生成主要包括步长、步速、步频等参数[9]。

四、观察指标

2 组患者均于训练前和训练 3 周后采用 PD 综合评分量表(unified Parkinson′s disease rating scale, UPDRS)[10]第Ⅱ部分和第Ⅲ部分评估 PD 患者的运动功能受损程度,采用 6 min 步行测试(six-minute walking distance,6MWD)评价患者的步行运动功能,同时采用 Berg 平衡量表(Berg balance Scale,BBS)评价患者的平衡功能。

五、统计学分析

采用 SPSS 17.0 版统计学软件进行分析,计量资料采用($\bar{x}\pm s$)表示,组内训练前、后比较采用 t 检验,组间比较采用方差检验。以$P<0.05$为差异有统计学意义。

结　果

研究过程中,听觉刺激组和对照组分别有 1 例和 2 例患者因各种原因退出研究。

治疗 3 周后,听觉刺激组步长和步频分别为(49.5±3.4)cm 和(88.7±8.1)步/分,与组内治疗前和对照组治疗后比较,差异均有统计学意义($P<0.05$)。治疗 3 周后,听觉刺激组的 UPDRS Ⅱ评分、UPDRS Ⅲ评分、6MWD 及 BBS 评分与组内治疗前和对照组治疗后比较,差异均有统计学意义($P<0.05$),详见表 2。

表 2　2 组患者训练前、后相关参数的比较($\bar{x}\pm s$)

组别	例数	步频(步/min)	步长(cm)	步速(cm/s)	UPDRS Ⅱ(分)	UPDRS Ⅲ(分)	6MWD(m)	BBS(分)
对照组								
治疗前	21	93.4±8.6	44.2±3.7	76.2±23.1	13.1±1.6	18.4±1.5	328.3±52.2	26.8±4.7
治疗后	19	93.1±9.4	45.5±3.8	76.5±19.6	12.9±1.3	18.6±1.3	327.5±49.7	27.2±4.4
听觉刺激组								
治疗前	21	93.7±8.4	45.3±4.2	75.3±21.6	13.5±1.2	18.7±1.6	327.3±49.2	26.3±4.5
治疗后	20	88.7±8.1^{ab}	49.5±3.4^{ab}	80.4±16.3^{ab}	11.8±1.7^{ab}	17.1±1.5^{ab}	353.5±46.8^{ab}	30.4±4.3^{ab}

注:与组内治疗前比较,$^{a}P<0.05$;与对照组治疗后比较,$^{b}P<0.05$

讨　论

多数 PD 患者都存在步态异常,轻者表现为出现启动迈步困难,出现拖行步态,并随着步行的继续而逐渐加剧[11];部分患者则表现为小碎步的慌张步态,行走时头和躯干前倾不能自控,下肢的髋、膝、踝关节的屈伸动作减少,使步幅减低,容易跌倒[12],且随病情加重,行走时步幅会逐渐缩短,行走时全身僵住呈冻结步态,最终可丧失行走能力。本研究采用节律性听觉刺激训练对 PD 患者进行步态训练,并进行了多指标评估,结果发现,节律性听觉刺激训练可改善 PD 患者的步态运动功能。

有研究发现,在 PD 早期,步频可在正常范围内略有减少,但随着病情的发展,步频可因姿势的改变而增加;PD 后期,患者可出现慌张步态,而表现步幅降低,步频增加[13]。该研究还指出,在 PD 后期采取策略降低 PD 患者的步频,可改善 PD 患者的步态功能。而节律性听觉刺激可减低 PD 患者的步频,减少其冻结次数,增加步幅,有利于改善患者的运动平衡功能。本研究结果显示,治疗 3 周后,听觉刺激组步长、步频、UPDRS Ⅱ评分、UPDRS Ⅲ评分、6MWD 及 BBS 评分与组内治疗前和对照组治疗后比较,差异均有统计学意义($P<0.05$)。提示节律性听觉刺激治疗改善 PD 患者步行运动及平衡功能。

节律性听觉刺激改善 PD 患者步行功能的因素可能包括以下几方面:①谐振效应——即两种事物之间的一种生物学的共振趋向。节律性听觉刺激可以接近步行固有的频率发放提示,患者可借助谐振效应来改善异常的步行节律[14]。②代偿作用——当 PD 患者基底核内部节律紊乱时,节律性听觉刺激可以通过其他没有被影响的路径,代偿基底核内部节律的缺陷,从而增强运动性能[15]。有研究指出,冻结步态的发生与额叶功能障碍、额叶和基底之间的联系中断有关,通过节律性刺激,PD 患者的右前小叶、小脑、齿状核及右侧颞顶叶交界处葡萄糖摄取增加[16],而小脑活动性的增加,可能意味着受损的基底核-辅助运动区-前额叶皮质路径得到补偿。因此,额叶功能障碍或额叶和基底神经节之间的联系中断,可被某些节律性刺激反射代偿,从而改善 PD 患者的步态。③精神放松作用——节律性听觉刺激尤其是音乐节拍的提示可在一定程度上解除患者的精神紧张因素,从而使其更轻松地完成步行[17]。④降低注意力需求——有研究表明,PD 患者的步态变异性大,跌倒风险增加,为防止跌倒,PD 患者在步行过程中要花较多的精力以保安稳,而节律性听觉刺激可通过减少步行变异率来增加步行的稳定性[18]。此外,节律性听觉刺激还可能使人在遇到复杂的任务时,将注意力集中,从而协助步态稳定[19]。

综上所述,节律性听觉刺激训练可辅助改善 PD 患者的步态,促进 PD 患者运动功能的恢复。但本研究尚有一定的局限性,如样本量有限,且由于受到 PD 患者住院天数的限制,训练时间仅为 3 周,观察时限较短。下一步课题组将开展多中心,大样本、长疗程研究以作进一步的探讨。

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·外刊撷英·

Vitamin D and changes in knee and hip pain

BACKGROUND AND OBJECTIVE Vitamin D deficiency is common among individuals with widespread bone and muscle pain, although this association may be biased, in that illness often leads to lower sun exposure. This study assessed the association between serum 25 hydroxy vitamin D and changes in knee and hip pain.

METHODS Data were obtained from the Tasmanian older adult cohort, a population-based study including men and women 50 to 80 years of age in 2002. Baseline data were obtained over two years, including 25-hydroxy vitamin D levels, as well as pain assessments using the Western Ontario and McMaster University Osteoarthritis (WOMAC) index questionnaire. All participants underwent x-ray examinations of the hips and knees, with films scored according to the Osteoarthritis Research Society International Atlas. Follow-up data were obtained at an average of 2.6 years and five years later.

RESULTS The prevalence of knee pain was 53% at baseline and 45% at five-year follow-up. Participants with moderate vitamin D deficiency experienced a greater worsening of total knee WOMAC pain scores over five years than did those above that level. The association with total hip WOMAC pain scores over 2.4 years did not reach statistical significance. When data were dichotomized, levels <25 nmol/L predicted incident or worsening pain according to total knee WOMAC scores, as compared with levels above this. Similar patterns were present in hip pain, although these findings did not reach statistical significance.

CONCLUSION This study suggests that a moderate vitamin D deficiency independently predicts change in knee pain over five years and, possibly, hip pain over 2.4 years.

【摘自:Laslett LL, Quinn S, Burgess JR, et al. Moderate vitamin D deficiency is associated with changes in knee and hip in older adults: A five-year, longitudinal study. Ann Rheum Dis, 2014, 73(4): 697-703.】

Vector based gene therapy for Parkinson's disease

BACKGROUND AND OBJECTIVE A crucial pathological component of Parkinson's disease (PD) is the progressive deterioration of dopaminergic neurons in the substantia nigra pars compacta. As the disease progresses, levodopa therapy becomes less effective. Gene therapy approaches using lentiviral vectors have been suggested as an option due to their low immunogenicity and high efficiency. This study assessed the efficacy of a lentiviral vector-based gene therapy (ProSavin) in restoring local and continuous dopamine production.

METHODS All subjects had bilateral idiopathic PD and were 48 to 65 years of age, with disease duration of at least five years. Three dose levels of ProSavin were assessed. The vector was administered bilaterally into the striatum under general anesthesia. The primary endpoints were the number and severity of adverse events, and motor responses, as assessed with the Unified Parkinson's Disease Rating Scale (UPDRS), administered six months after vector administration. The participants were clinically assessed weekly during the first month and at one, two, three, six, 12 months.

RESULTS Of the 15 patients followed, three received dose level I, six dose level II and six dose level III. Eight serious events were noted, and determined to be unrelated to the study drug. The most common drug related adverse events were increased on-medication dyskinesias, and on-off phenomena. The UPDRS motor scores were significantly improved as compared with baseline at six months and at 12 months in all 15 patients ($P=0.0001$ for both). No significant differences were found among different dose cohorts.

CONCLUSION This study found that a lentivirus vector-based gene therapy is safe, and can improve motor behavior in patients with Parkinson's disease.

【摘自:Palfi S, Gurruchaga JM, Ralph GS, et al. Long-term safety and tolerability of prosavin, a lentiviral vector based gene therapy for Parkinson's disease: A dose escalation, open label, phase 1/2 trial. Lancet, 2014, 29(9923): 1138-1146.】