·综述与讲座·

低频脉冲电磁场治疗神经系统疾病的研究进展

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［摘要］ 低频脉冲电磁场是一种无创且安全的物理治疗方法。目前主要用于骨折、骨关节炎、股骨头坏死、骨质疏松以及软骨损伤等的临床辅助治疗。最近有研究表明，除了具有促进骨折愈合、加速软骨细胞的增殖、增加骨密度等作用外，低频脉冲电磁场还能够有效地治疗和改善多种神经系统相关疾病及其神经损伤症状。本文就近年来脉冲电磁场对脑卒中、帕金森病以及多发性硬化的疗效和相关机制进行综述，以期为临床上该类疾病的治疗提供一些新思路。

［关键词］ 脉冲电磁场；脑卒中；帕金森病；多发性硬化

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Progress of Low Frequency Pulsed Electromagnetic Fields against Neurological Disease

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Abstract：Low frequency pulsed electromagnetic fields is a non-invasive and safe physical therapy，and it has been used as a clinical adjuvant treatment of bone fracture，osteoarthritis，femur head necrosis，osteoporosis and cartilage injury. In addition to the effect of promoting fracture healing and the proliferation of chondrocytes，and increasing bone density，recent researches have shown that low frequency pulsed electromagnetic fields have the potential to treat neurological disease and ameliorate nerve injury symptoms. Therefore，this paper reviewed the progress of efficacy and mechanism of low frequency pulsed electromagnetic fields on stroke，Parkinson's disease and multiple sclerosis，so as to provide some new idea for the treatment of the diseases.

Key words： low frequency pulsed electromagnetic fields；stroke；Parkinson's disease；multiple sclerosis

脉冲电磁场（pulsed electromagnetic field，PEMF）作为一种无创的物理干预方式，最早用于骨不连和骨折延迟愈合的治疗[1]。PEMF是由电流通过赫尔姆兹线圈所产生的具有脉冲间歇的磁场效应。PEMF装置主要由三部分组成，第一部分为信号发生器，它能够产生具有特定波形和频率的电压信号；第二部分为信号扩大器，它能够产生供应电磁场发生器的电流输出，调节扩大器的输出可以改变场强的大小。第三部分为电磁场发生器，它主要由线圈组成。通过电容和电感的方式，PEMF可无创地作用于生物系统。前者需要将相对电极放置在感兴趣组织周围，并且与皮肤直接接触，而后者则无需接触皮肤[2]。低频脉冲电磁场（low frequency pulsed electromagnetic field，LF-PEMF）作为低频电磁场的代表，是指频率为1~100 Hz，峰值磁场<10 mT的低频、低强度磁场。近年来被越来越多地应用于神经系统疾病的治疗，现就LF-PEMF对脑卒中、帕金森病、多发性硬化的治疗作用综述如下。

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1 脉冲电磁场用于脑卒中治疗的研究

脑卒中是神经系统的常见疾病，具有发病率高、病死率高以及致残率高等特点，严重影响患者的生活质量，是当今社会面临的重大公共健康问题。有研究表明，炎症在脑卒中的发展与转归过程扮演了重要的角色。脑卒中后，神经胶质细胞被激活，伴随着炎症细胞因子的产生以及单核细胞的浸润[3]。其中，白介素1(interleukin-1，IL-1)是研究最为广泛的一种炎症相关细胞因子，它主要有两种不同的分子形式，即IL-1α和IL-1β，与之结合的受体同样存在两种形式，即白介素1受体Ⅰ型(IL-1 receptor typeⅠ，IL-1RⅠ)和白介素1受体Ⅱ型(IL-1 receptor type Ⅱ，IL-1RⅡ)。在脑缺血的早期，IL-1β大部分由激活的小胶质细胞释放，后期则主要由巨噬细胞释放[4]。Toll样受体的活化引起前体蛋白(IL-1β precursor，pIL-1β)mRNA的表达，当出现组织损伤或者微生物入侵的时候，半胱天冬酶1裂解pIL-1β为具有活性的IL-1β，从而发挥其生物学功能[5]。既往的研究表明，脑卒中后IL-1β的增高会引起梗塞灶的扩大并加重神经功能的缺损，但当给予IL-1R拮抗剂(IL-1R antagonist，rhIL-1Ra)后，上述指标出现了明显的改善[6]。另一种细胞因子肿瘤坏死因子(tumor necrosis factor，TNF)分为TNF-α和TNF-β，在脑组织内通常由区别于释放IL-1的不同亚型小胶质细胞和巨噬细胞分泌[4]，并通过与膜表面受体TNF-R1和TNF-R2结合发挥其生物学功能[7]。Awooda等的研究发现，与对照组相比，实验组的大鼠在脑卒中后无论是脑组织或者血清的TNF-α水平均明显增高，并且其增高的水平与梗塞面积的大小成反比，表明TNF-α在神经元的损伤过程中扮演了重要的角色[8]。相比之下，另外两种细胞因子IL-6和IL-10则具有神经保护作用。IL-6被证实可以改善脑卒中所致的学习障碍，延迟神经元的丢失[9]，减轻缺血性脑损伤[10]。IL-10作为一种抗炎性细胞因子，无论是基础研究或是临床试验均表明其对缺血性脑卒中具有保护作用[11-12]。上述的炎症细胞因子在脑卒中的进展过程中扮演了重要的角色，是脑卒中治疗的潜在靶点。Pena-Philippides等通过研究发现，给予大脑中动脉模型实验组C57BL/6小鼠为期21天，1天2次，每次15分钟的LF-PEMF治疗[2 Hz，信号振幅(3±0.6) V/m]，对照组给予相同参数的假刺激。结果表明，与对照组相比，LF-PEMF不仅能减少实验组小鼠的梗塞面积，并且可以降低促炎性因子IL-1α的基因表达，增加抗炎性因子IL-10的表达。另外，LF-PEMF还能下调促凋亡TNF超家族的基因编码，从而从抗炎和抗凋亡两个角度影响脑卒中后的恢复进程[13]。该研究与Urnukhsaikhan等的实验结果一致[14]。但目前仅有2项研究探讨了LF-PEMF对于炎症因子的影响，除去以上细胞因子，还有诸如氧自由基、NO和NO合成酶甚至粘附分子等，LF-PEMF对上述物质是否同样具有调控作用有待深入的研究。Bates的团队采用自发性高血压大鼠，通过线栓法制备再灌注大脑中动脉梗塞模型后随机分为四个组：实验组在再灌注后的1小时和24小时接受为期6天、每天10分钟的患侧LF-PEMF(20 Hz，8 mT)治疗，而对照组不接受任何刺激。实验组再进一步划分为三个组，其中一组在再灌注后48小时接受患侧20 Hz假刺激，第二组在相同时间点接受健侧1 Hz LF-PEMF治疗，而最后一组则接受患侧6~9 Hz LF-PEMF治疗。结果发现，与对照组相比，三个LF-PEMF实验组在降低梗塞面积和改善神经功能等方面差异均无统计学意义[15]。造成以上研究结果的差异可能是由于治疗参数以及造模方法等的不同所导致，因此，需要更多的实验以进一步探寻LF-PEMF用于脑卒中治疗的最佳参数。

除去对炎症因子的影响，LF-PEMF还可能通过调控神经递质如腺苷和谷氨酸的受体[16-17]，减少中枢神经系统组织钙的外流[18]，加速脑源性神经营养因子的产生(brain-derived neurotrophic factor，BDNF)[19]等机制影响脑卒中的恢复。目前，一项关于LF-PEMF用于脑卒中治疗的双盲随机对照研究正在进行当中，相信未来还会有更多证据更新或者支持LF-PEMF用于脑卒中的治疗。

2 脉冲电磁场用于帕金森病治疗的研究

帕金森病(Parkinson's disease，PD)是一种以黑质多巴胺能神经元选择性进行性丢失为病理特征的常见神经系统退行性疾病。中国的患病率约为79.5/1 000 000至193.3/1 000 000[20]，临床上主要表现为静止性震颤、运动迟缓、肌强直和姿势步态障碍。帕金森病的病因至今尚不十分明确，可能与遗传因素、环境因素以及老化有关，其发病机制也涉及氧化应激、炎症、谷氨酸兴奋性毒性以及神经营养因子缺乏等。

谷氨酸能神经元功能障碍被认为是引起帕金森病神经性炎症和多巴胺能神经元变性的重要机制[21]。90%的谷氨酸被谷氨酸转运体摄取，这种转

运体广泛分布于星形胶质细胞,对于调节突触中的谷氨酸浓度具有重要作用。既往的研究已证实PD会出现谷氨酸转运体蛋白的表达减少[22]。过度释放的谷氨酸能刺激另一种受体NMDA(N-methyl-D-aspartic acid)受体的兴奋并引起钙超载,最终导致神经炎症和神经细胞的死亡[23]。此外,BDNF作为一种具有神经营养作用的蛋白质,在脑组织中的海马和皮质具有较高含量[24]。BDNF一方面对于黑质中的多巴胺能神经元具有神经保护作用[25],另一方面,BDNF还可通过调控神经递质如谷氨酸和γ-氨基丁酸的代谢影响突触可塑性[26],且无论是基础研究还是临床试验均证实其与PD的联系密切[27-29]。LF-PEMF作为一种新兴的无创的刺激技术,不仅能调控BDNF[30]和谷氨酸[17]的代谢,并且还能促进轴突的生长[31]以及减轻神经炎症[13]。因此,可用于PD的治疗。既往的研究发现,LF-PEMF可以改善PD患者的冻结步态[32]、偏侧忽略[33],提高PD患者对于左旋多巴的反应[34],但研究多以个案报道为主。近期,Morberg等进行的一项随机双盲对照研究发现,给予实验组为期8周、每天30分钟的经颅LF-PEMF(50 Hz,5~8 mT)治疗,结果表明,与接收假刺激的对照组相比,两组帕金森病综合评分量表(unified Parkinson's disease rating scale,UPDRS)的评分差异无统计学意义[35]。造成该结果的原因可能是量表的选择以及刺激的深度和时长不足所致,该研究已调整其治疗参数以进行进一步的研究。

3 脉冲电磁场用于多发性硬化治疗的研究

多发性硬化(multiple sclerosis,MS)是一种以中枢神经系统白质炎症性脱髓鞘病变为主要病理特征的免疫介导性疾病。MS的起病年龄多在20~50岁,其临床症状和体征多变,可表现为运动功能障碍、感觉功能障碍、眼部症状、平衡功能障碍、认知功能障碍、精神症状、疼痛以及疲劳等,严重影响了患者的生活质量。

MS的病因和发病机制至今尚未完全明确,有研究表明MS与N-乙酰天冬氨酸水平降低,谷氨酸、天冬氨酸等兴奋性氨基酸水平升高[36-37],下丘脑-垂体-肾上腺系统功能失调等有关[38],而电磁场被证实对多种神经化学物质均具有调控作用[39]。另外,Mohammad等的研究还发现电磁场可促进神经干细胞的增殖和迁移,加速髓鞘的修复[40],因此对于MS,电磁场可能具有潜在的治疗功效。早期的研究证实LF-PEMF可以改善MS患者的偏侧忽略、构音障碍以及震颤等症状[41-43],2006年发表的一项荟萃分析也表明对于改善MS患者的疲劳现象,LF-PEMF是一项很有前景的治疗方法[44]。2011年的一篇探索LF-PEMF对于MS患者长期疗效的研究也证实了该种疗法的有效性[45]。但即便如此,由于方法学和试验例数的限制,LF-PEMF用于MS的治疗仍需进一步的研究和调查。

4 总结与展望

LF-PEMF作为一种无创的物理治疗方法,其用于肌肉骨骼系统的疗效已得到肯定,但PEMF对于神经系统的作用尚处于探索的阶段。虽然基础研究表明LF-PEMF可以减轻炎症反应,促进轴突的生长,调控多种神经化学物质,且临床试验也初步证实了其疗效,然而,对于LF-PEMF治疗神经系统疾病的研究仍需注意以下几点:①目前关于LF-PEMF在神经系统的应用多以病案报道和小样本的临床研究为主,因此,为了获得更加准确可靠的实验结果,未来需要更多大样本、优化设计的研究以进一步验证其疗效。②由于LF-PEMF的疗效与刺激的频率、强度、时间以及刺激的部位密切相关,对于最佳的治疗参数范围还需更深入的探索。③长期使用PEMF是否存在可能的安全问题值得进一步的研究。

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研究也存在样本例数仍需扩大、未能获得其他抗体进行比较、未能在Ventana等自动化平台上分析、未能与临床疗效进行关联分析等不足之处。在下一步研究中,我们将采用该检测方法与临床免疫治疗效果相结合研究其应用价值。

综上,本研究提供了临床标本验证的PD-L1表达免疫组织化学方法,发现SP142和E1L3N两种抗体在检测我国非小细胞肺癌标本中肿瘤细胞比例(TPS)具有较好的一致性。对于免疫细胞的检测分析解读需要进一步研究。鉴于部分标本只能被一种抗体检测为阳性,所以两种抗体联合应用检测具有互补性,可能有助于检测出更多阳性患者用于临床治疗参考。

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