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认知康复训练联合高频重复经颅磁刺激对脑卒中后认知障碍患者 认知功能和血清 BDNF、VEGF 的影响 *

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摘要 目的:观察脑卒中后认知障碍(PSCI)患者在认知康复训练基础上辅助高频重复经颅磁刺激(rTMS)治疗后,其认知功能和血清脑源性神经营养因子(BDNF)、血管内皮生长因子(VEGF)水平变化。**方法:**选择我院 2020 年 1 月~2020 年 12 月期间接收的 300 例 PSCI 患者,以随机数字表法将患者分为实验组(150 例)、对照组(150 例)。对照组在常规治疗基础上联合认知康复训练,实验组则在对照组的基础上联合高频 rTMS。对比两组认知功能、日常生活能力、听觉事件相关电位、血清 BDNF 和 VEGF 水平及不良反应。**结果:**两组治疗 4 周后蒙特利尔认知评估量表(MoCA)各条目评分及总分均较治疗前升高,且实验组高于对照组($P<0.05$)。两组治疗 4 周后改良 Barthel 指数(MBI)评分较治疗前升高,且实验组高于对照组($P<0.05$)。实验组治疗 4 周后 P300 潜伏期短于对照组,P300 波幅高于对照组($P<0.05$)。两组治疗 4 周后血清 BDNF、VEGF 水平升高,且实验组高于对照组($P<0.05$)。两组不良反应发生率组间对比无统计学差异($P>0.05$)。**结论:**认知康复训练联合高频 rTMS 可有效改善 PSCI 患者认知功能,上调其血清 BDNF、VEGF 水平,改善听觉事件相关电位,从而提高患者日常生活能力。

关键词:认知康复训练;高频;重复经颅磁刺激;脑卒中后认知障碍;认知功能;脑源性神经营养因子;血管内皮生长因子
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Effects of Cognitive Rehabilitation Training Combined With High Frequency Repetitive Transcranial Magnetic Stimulation on Cognitive Function and Serum BDNF, VEGF in Patients with Post-Stroke Cognitive Impairment*

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ABSTRACT Objective: To observe the changes of cognitive function and serum levels of brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) in patients with post-stroke cognitive impairment (PSCI) after cognitive rehabilitation training combined with high frequency repetitive transcranial magnetic stimulation (rTMS). **Methods:** 300 patients with PSCI who were received in our hospital from January 2020 to December 2020 were selected, and they were randomly divided into experimental group (150 cases), control group (150 cases) by the random number table method. The control group was combined with cognitive rehabilitation training on the basis of conventional treatment, while the experimental group was combined with high-frequency rTMS treatment on the basis of the control group. The cognitive function, ability of daily life, auditory event-related potential, serum BDNF and VEGF levels and adverse reactions of the two groups were compared. **Results:** 4 weeks after treatment, the items and total scores of Montreal Cognitive Assessment Scale(MoCA) in the two groups were higher than those before treatment, and the experimental group was higher than the control group ($P<0.05$). 4 weeks after treatment, the modified Barthel index (MBI) score in the two groups was higher than that before treatment, and the experimental group was higher than the control group ($P<0.05$). 4 weeks after treatment, the incubation period of P300 in the experimental group was shorter than that in the control group, and the amplitude of P300 was higher than that in the control group ($P<0.05$). 4 weeks after treatment, serum BDNF and VEGF levels in the two groups increased, and the experimental group were higher than the control group ($P<0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Cognitive rehabilitation training combined with high frequency rTMS can effectively improve the cognitive function of patients with PSCI, up regulate the BDNF and VEGF levels, improve auditory event-related potential, and improve the ability of daily life of patients.

Key words: Cognitive rehabilitation training; High frequency; Repetitive transcranial magnetic stimulation; Post-stroke cognitive impairment; Cognitive function; Brain derived neurotrophic factor; Vascular endothelial growth factor

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前言

认知障碍是脑卒中患者常见的并发症之一,发生率约为20%~80%,脑卒中后认知障碍(PSCI)除了影响患者日常活动外,还会增加患者病死率,降低患者生存质量^[1,2]。目前PSCI未能够得到临床足够的重视,其治疗方案也未能统一,目前临床上针对PSCI的治疗手段主要有药物治疗和非药物治疗,药物治疗短期内收益较好,长期应用不良反应大,患者依从性降低,治疗效果一般^[3,4];非药物治疗如认知康复训练已被不少研究证实具备有效性,但也存在费时费力、认知障碍的患者配合度较差等问题^[5]。高频重复经颅磁刺激(rTMS)是一种新型无创性神经电生理刺激技术,高频rTMS可通过调节突触可塑性产生长时程增强,从而影响局部及远隔区域神经功能^[6,8]。本研究通过观察高频rTMS联合认知康复训练对PSCI患者的影响,以期为临床治疗方案选择提供理论支持。

1 资料与方法

1.1 一般资料

选择我院2020年1月~2020年12月期间接收的300例PSCI患者,入组患者家属均签署知情同意书,PSCI的诊断标准参考《卒中后认知障碍管理专家共识》^[9],研究方案得到我院伦理学委员会批准进行。纳入标准:(1)均为首发脑卒中,经头颅计算机断层扫描(CT)或磁共振成像(MRI)证实,生命体征稳定;(2)神志清醒,可配合相关治疗者;(3)蒙特利尔认知评估量表(MoCA)^[10]评分 ≤ 24 分;(4)病程1个月以上,患者年龄40~70岁。排除标准:(1)发病前存在认知功能障碍者;(2)有高频rTMS治疗禁忌者;(3)合并心肝肾等重要器官功能不全者;(4)既往有脑出血、癫痫、脑外伤等病史者;(5)发病前有酒精、药物依赖史者;(6)病情恶化,出现新的出血灶或梗死灶。分组方法选用随机数字表法,分为对照组和实验组,各150例。对照组男性86例、女性64例,平均年龄 (61.59 ± 5.82) 岁;平均病程 (2.51 ± 0.48) 月;平均MoCA评分 (17.74 ± 0.36) 分;脑卒中类型:脑出血96例、脑梗死54例。实验组男性81例、女性69例,平均年龄 (61.14 ± 4.97) 岁;平均病程 (2.47 ± 0.36) 月;平均MoCA评分 (17.78 ± 0.45) 分;脑卒中类型:脑出血91例、脑梗死59例。两组患者一般资料组间对比差异无统计学意义($P>0.05$),均衡可比。

1.2 方法

两组均予以常规基础治疗,包括改善微循环、营养神经、抗凝等。同时进行常规康复训练,包括床上、坐位、站位、步行、平衡、上肢及功能训练等。常规康复训练每周5次,40 min/次,休息2 d后进行下一周的治疗,共训练4周。在此基础上,对照组接受认知康复训练,具体为:采用回忆图片序列、短文背诵、图片记忆等方法训练记忆力;通过对患者空间、时间、人物的感知训练定向力;用猜测游戏、连续数数、视觉追踪等方法训练注意力;通过制作手工物品等方式训练执行能力;通过摆积木、采用下棋、拼图等方法训练视觉空间结构;通过设定日常生活场景等方式训练思维推理;通过看图找差别等方式训练判断推理。认知康复训练每周5次,1 h/次,休息2 d后进行下一周的治疗,共训练4周。实验组在对照组基础上结合高频rTMS治疗,

每周5次,20 min/次,休息2 d后进行下一周的治疗,共治疗4周。患者取卧位,选用HX-C3型rTMS经颅磁治疗仪(购自上海三崴医疗设备有限公司),磁刺激线圈平面与颅骨表面相切,磁刺激频率为10 Hz,磁刺激强度为80%运动阈值,每刺激2 s间隔20 s。

1.3 观察指标

1.3.1 认知功能 治疗前、治疗4周后采用MoCA评估患者认知功能,MoCA包括命名、抽象概况、注意力、视空间及执行功能、延迟回忆、定向、言语等条目,MoCA总分为30分,分数越高,认知功能越好^[10]。

1.3.2 日常生活能力 治疗前、治疗4周后采用改良Barthel指数(MBI)^[11]评分评估患者的日常生活能力,MBI评分总分100分,分数越高日常生活能力越高。

1.3.3 P300潜伏期、波幅 观察两组患者治疗前后听觉事件相关电位P300波的潜伏期与波幅。检测方法:检测时患者保持觉醒状态,静坐于检查椅上,采用VikingQuest4通道台式肌电诱发电位系统(美国尼高力仪器公司生产)的听觉Oddball程序,电极与皮肤之间电阻 $<5 \text{ k}\Omega$,分析时间100 ms,灵敏度 $5 \mu\text{V}$ 。同时VikingQuest4通道台式肌电诱发电位系统自动记录P300波幅和潜伏期。重复检查3次,取平均值。

1.3.4 实验室指标 治疗前、治疗4周后抽取两组患者清晨空腹静脉血5 mL,离心分离血清。采用酶联免疫吸附法检测血清脑源性神经营养因子(BDNF)、血管内皮生长因子(VEGF)水平,试剂盒均购自上海江莱生物科技有限公司,实验步骤严格按照说明书进行。

1.3.5 不良反应 观察治疗过程中的安全性。

1.4 统计学方法

本研究收集的所有数据均采用SPSS20.0统计软件进行分析。P300潜伏期、MoCA各条目评分等计量资料经检验符合正态分布,以 $(\bar{x} \pm s)$ 表示,组内、组间比较分别采取配对t检验和成组t检验。不良反应发生率等计数资料以比或率表示,行卡方检验。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 认知功能对比

两组治疗4周后MoCA各条目评分及总分较治疗前升高,且实验组高于对照组($P<0.05$),见表1。

2.2 日常生活能力对比

两组治疗前MBI评分组间对比无明显差异($P>0.05$),两组治疗4周后MBI评分较治疗前升高,且实验组高于对照组($P<0.05$),见表2。

2.3 P300潜伏期、波幅对比

两组治疗前P300潜伏期、P300波幅组间对比差异无统计学意义($P>0.05$),两组治疗4周后P300潜伏期缩短,P300波幅升高($P<0.05$),实验组治疗4周后P300潜伏期短于对照组,P300波幅高于对照组($P<0.05$),见表3。

2.4 两组患者血清BDNF、VEGF水平对比

两组治疗前血清BDNF、VEGF水平对比无明显差异($P>0.05$),两组治疗4周后血清BDNF、VEGF水平升高,且实验组高于对照组($P<0.05$),见表4。

表 1 认知功能对比($\bar{x} \pm s$, 分)

Table 1 Comparison of cognitive function($\bar{x} \pm s$, scores)

Groups	Times	Name	Visual space and execution function	Attention	Speech	Delayed recall	Directional	Abstract overview	Total scores
Control group (n=150)	Before treatment	2.39± 0.31	2.41± 0.27	3.13± 0.25	2.13± 0.28	2.66± 0.34	4.11± 0.36	0.91± 0.09	17.74± 0.36
	4 weeks after treatment	2.88± 0.37 ^a	2.93± 0.26 ^a	3.56± 0.32 ^a	2.69± 0.23 ^a	3.08± 0.31 ^a	4.53± 0.33 ^a	1.22± 0.08 ^a	20.89± 0.44 ^a
Experi- men- tal group (n=150)	Before treatment	2.41± 0.25	2.42± 0.32	3.16± 0.34	2.11± 2.29	2.63± 0.27	4.13± 0.42	0.92± 0.11	17.78± 0.45
	4 weeks after treatment	3.35± 0.29 ^{ab}	3.55± 0.39 ^{ab}	4.04± 0.37 ^{ab}	3.19± 0.34 ^{ab}	3.57± 0.29 ^{ab}	5.06± 0.38 ^{ab}	1.66± 0.14 ^{ab}	24.42± 0.39 ^{ab}

Note: a compared with before treatment, $P<0.05$. b compared with the control group, $P<0.05$.

表 2 日常生活活动评分对比($\bar{x} \pm s$, 分)

Table 2 Comparison of activities of daily living scores($\bar{x} \pm s$, scores)

Groups	Before treatment	4 weeks after treatment
Control group(n=150)	51.24± 6.19	66.72± 7.38 ^a
Experimental group(n=150)	51.45± 5.23	78.99± 6.24 ^a
t	-0.317	-15.749
P	0.751	0.000

Note: a compared with before treatment, $P<0.05$.

表 3 P300 潜伏期、波幅对比($\bar{x} \pm s$)

Table 3 Comparison of incubation period and amplitude of P300($\bar{x} \pm s$)

Groups	Times	Incubation period of P300(ms)	Amplitude of P300(μV)
Control group(n=150)	Before treatment	398.71± 23.52	5.38± 0.49
	4 weeks after treatment	356.68± 25.41 ^a	7.84± 0.31 ^a
Experimental group(n=150)	Before treatment	397.42± 22.67	5.32± 0.33
	4 weeks after treatment	321.24± 24.53 ^{ab}	9.75± 0.48 ^{ab}

Note: a compared with before treatment, $P<0.05$. b compared with the control group, $P<0.05$.

表 4 两组患者血清 BDNF、VEGF 水平对比($\bar{x} \pm s$)

Table 4 Comparison of serum BDNF and VEGF levels between the two groups($\bar{x} \pm s$)

Groups	Times	BDNF(ng/mL)	VEGF(pg/mL)
Control group(n=150)	Before treatment	4.91± 0.72	72.62± 2.58
	4 weeks after treatment	6.96± 1.13 ^a	109.43± 8.44 ^a
Experimental group(n=150)	Before treatment	4.87± 0.66	72.19± 2.43
	4 weeks after treatment	8.24± 1.27 ^{ab}	163.98± 10.39 ^{ab}

Note: a compared with before treatment, $P<0.05$. b compared with the control group, $P<0.05$.

2.5 不良反应发生率对比

对照组治疗期间未发生不良反应,不良反应发生率 0.00%(0/150);实验组治疗期间有 3 例出现轻微头疼、头晕,未进行任何处理的情况下数日内均自行缓解,不良反应发生率为 2.00%(3/150)。两组不良反应发生率组间对比无统计学差异($\chi^2=3.030$, $P=0.082$)。

3 讨论

认知功能包括计算、记忆、执行、时空定向等多个领域,这些领域出现行为障碍会给患者带来沉重的心理负担,影响患者后期康复进程^[12-14]。PSCI 的发病原因和发病机制较为复杂,主要与以下因素有关:关键部位如额叶内侧区、前额叶区、颞叶海马区等区域发生卒中;中枢神经传导通路受损也会导致认知功能障碍出现;脑卒中发病后产生一系列的氧化应激、炎症反应和某些有害物质的沉积等;遗传、年龄和急性脑血管事件的发生^[15-17]。因此,清晰了解与认知功能相关的解剖部位,以及脑卒

中发病后,与认知相关神经递质的分泌情况,对于 PSCI 的治疗具有重要的参考意义。认知康复训练主要是针对于某一方面的认知功能缺陷进行的训练,可在一定程度上恢复患者认知功能,但缺乏趣味性,且患者不一定能顺利完成整套康复训练,尚存在一些不足^[18]。

近年来的研究发现^[19],rTMS 可促进阿尔兹海默病及血管性认知障碍患者认知功能的恢复。另有研究还发现^[6,8],高频率的 rTMS 能够显著提高大脑皮质的兴奋性。本研究在认知康复训练基础上联合高频 rTMS 治疗 PSCI 患者,并以单纯认知康复训练作为对照,结果显示,辅助高频 rTMS 治疗可有效改善 PSCI 患者认知功能,改善日常生活能力。rTMS 的主要作用机理在于电磁脉冲可刺激大脑皮质神经元细胞电位产生改变,并随之产生感应电流,从而兴奋周围更多神经元细胞,有利于大脑皮质网络功能重建,从而促进认知功能恢复^[20-22]。PSCI 患者日常生活能力的提高往往取决于认知功能的提高,认知功能恢复越好患者自控能力越佳,有利于其后续参加康复训练,形成良性循环^[23]。此外,随着认知功能的改善,其网络连通性不断修复,从而有效促进日常生活能力的提高^[24]。听觉事件相关电位属于临床常见的电生理检查指标,常被用于评估机体大脑认知功能^[25]。现有的研究认为^[26],存在认知功能障碍的患者其 P300 波幅下降,P300 潜伏期延长。一般情况下,潜伏期越短,波幅越高,患者认知功能越好。本次研究中,实验组治疗 4 周后 P300 潜伏期短于对照组,P300 波幅高于对照组,说明认知康复训练联合高频 rTMS 治疗可有效改善 PSCI 患者听觉事件相关电位。高频 rTMS 具有储存功能电容的作用,利用电生磁和磁生电的原理,形成新的传导通路,进而兴奋刺激部位的神经,有效缩短 P300 潜伏期,提高 P300 波幅^[27,28]。VEGF 作为脑内营养因子之一,可促进脑血管新生^[29]。BDNF 参与脑组织损伤后神经修复过程,可有效调节神经可塑性,并发挥修复神经功能的作用^[30]。本研究结果显示实验组治疗 4 周后血清 BDNF、VEGF 水平高于对照组,可见高频 rTMS 可刺激 BDNF、VEGF 等细胞因子分泌,修复受损脑组织,主要是因为高频 rTMS 可增加突触可塑性,促进突触间发挥传递功能,从而促进 VEGF、BDNF 分泌^[31]。疼痛、头晕、皮肤过敏、耳鸣等是高频 rTMS 治疗期间常见的不良反应,本次研究中实验组仅出现 3 例轻微头疼、头晕症状,且未影响治疗进程,提示高频 rTMS 治疗仍属于一种较为安全的治疗方式,有利于临床持续进行。

综上所述,认知康复训练联合高频 rTMS 治疗 PSCI 患者,可有效提高其血清 BDNF、VEGF 水平,改善听觉事件相关电位,促进认知功能恢复,从而提高患者日常生活能力。本次研究的不足之处在于未对高频 rTMS 治疗的最佳周期及刺激部位进行深入分析,有待在后续研究中进行改进。

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(上接第 485 页)

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