

• 临床研究 •

超低频经颅磁刺激治疗儿童孤独症谱系障碍合并睡眠障碍的临床研究

李诺, 周园, 钱旭光, 刘振寰, 庞碧微, 徐立宝, 姚向歌, 赵勇

广州中医药大学附属南海妇产儿童医院儿童康复科, 广东 佛山 528200

摘要: **目的** 探讨超低频经颅磁刺激(ILF-TMS)联合常规康复训练对孤独症谱系障碍(ASD)合并睡眠障碍儿童的治疗效果,为临床治疗提供科学依据。**方法** 选择 2023 年在广州中医药大学附属南海妇产儿童医院就诊的 60 例 ASD 合并睡眠障碍儿童为研究对象,采用随机数表法分为研究组与对照组,各 30 例。对照组接受应用行为分析法、感觉统合训练和言语治疗等常规康复训练,研究组给予 ILF-TMS,两组均治疗 12 周,治疗前后采用儿童睡眠习惯问卷(CSHQ)、孤独症行为量表(ABC)和儿童孤独症评定量表(CARS)评估,并对两组各指标进行组内比较及治疗前后差值的组间比较,以观察治疗效果。**结果** 研究组治疗后在 CSHQ 评分中睡眠阻抗、睡眠焦虑、睡眠时间、异态睡眠、日间困倦得分及总分较治疗前明显降低($t=2.438, 2.261, 2.295, 2.987, 5.954, 5.518, P<0.05$),且治疗前后得分差值显著高于对照组,差异有统计学意义($t=2.201, 2.218, 2.604, 3.322, 6.668, 8.216, P<0.05$);研究组、对照组治疗后 CARS、ABC 总分均较治疗前显著降低(研究组: $t=3.067, 3.125$;对照组: $t=2.098, 2.094, P<0.05$),研究组 ABC 总分治疗前后的差值显著大于对照组,差异有统计学意义($t=3.121, P<0.05$)。**结论** ILF-TMS 可有效改善 ASD 儿童的睡眠障碍,并减轻其临床症状,为 ILF-TMS 在 ASD 患儿治疗中的应用提供理论依据。

关键词: 超低频经颅磁刺激;孤独症谱系障碍;睡眠障碍

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Efficacy of infra-low frequency transcranial magnetic stimulation on the treatment of autism spectrum disorder combined with sleep disorder in children

LI Nuo, ZHOU Yuan, QIAN Xuguang, LIU Zhenhuan, PANG Bihui, XU Libao, YAO Xiangge, ZHAO Yong

Department of Children's Rehabilitation, Nanhai Obstetrics and Gynecology Children's Hospital

Affiliated to Guangzhou University of Traditional Chinese Medicine, Foshan, Guangdong 528200, China

Corresponding author: ZHAO Yong, E-mail: Innhfy@126.com

Abstract: **Objective** To investigate the therapeutic efficacy of infra-low frequency transcranial magnetic stimulation (ILF-TMS) combined with conventional rehabilitation training in children with autism spectrum disorder (ASD) and comorbid sleep disturbances, in order to provide a scientific basis for clinical treatment. **Methods** A total of 60 children with ASD and sleep disturbances, who were treated at the Nanhai Obstetrics and Gynecology Children's Hospital Affiliated to Guangzhou University of Traditional Chinese Medicine in 2023, were selected as study participants. They were randomly divided into a study group and a control group using a random number table, with 30 children in each group. The control group received conventional rehabilitation training, including applied behavior analysis therapy, sensory integration training, and speech therapy. The study group received ILF-TMS additionally. Both groups underwent treatment for 12 weeks. The Children's Sleep Habits Questionnaire (CSHQ), Autism Behavior Checklist (ABC), and Childhood Autism Rating Scale (CARS) were used to assess outcomes before and after treatment. Intra-group comparisons and inter-group comparisons of score changes before and after treatment were conducted to evaluate therapeutic effects. **Results** In the study group, post-treatment scores for sleep resistance, sleep anxiety, sleep duration, parasomnias, daytime sleepiness, and total CSHQ scores were significantly lower than pre-treatment scores ($t=2.438, 2.261, 2.295, 2.987, 5.954, 5.518, P<0.05$). Moreover, the differences in the above score changes before and after treatment were significantly greater in the study group compared to the control group, with statistical significance ($t=2.201, 2.218, 2.604, 3.322, 6.668, 8.216,$

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作者简介:李诺(1980—),主任医师,本科学历,主要从事儿童神经系统疾病康复方面的研究。

通信作者:赵勇, E-mail: Innhfy@126.com

$P < 0.05$). Both the study and control groups showed significant reductions in CARS and ABC total scores after treatment (study group: $t = 3.067, 3.125$; control group: $t = 2.098, 2.094, P < 0.05$). The difference in ABC total score changes before and after treatment was significantly greater in the study group compared to the control group ($t = 3.121, P < 0.05$).

Conclusions ILF-TMS can effectively improve sleep disturbances and alleviate clinical symptoms in children with ASD, which provides theoretical support for the application of ILF-TMS in the treatment of children with ASD.

Keywords: infra-low frequency transcranial magnetic stimulation; autism spectrum disorder; sleep disorder

孤独症谱系障碍 (autism spectrum disorder, ASD) 是一种复杂的神经发育障碍性疾病, 以社会交往和沟通障碍、狭隘兴趣与刻板重复行为为主要特征^[1]。ASD 发病率高, 阻碍患儿心理行为及社交能力的发育, 同时常常共患睡眠障碍、情绪障碍、智力发育障碍等诸多疾病, 其中合并睡眠障碍者占 44%~80%^[2], 严重影响患儿及其家庭的生活质量。目前干预方式以心理或行为干预为主, 耗时长, 对家庭康复要求高。近年来, 超低频经颅磁刺激 (infra-low frequency transcranial magnetic stimulation, ILF-TMS) 作为一种新兴的非侵入性脑刺激技术, 起初用于失眠和抑郁症的治疗, 近年逐渐应用于神经康复和精神康复领域^[3]。本研究旨在探讨 ILF-TMS 对 ASD 患儿睡眠障碍及核心症状的改善作用, 为临床治疗提供新的思路和方法。

1 对象和方法

1.1 对象 选择 2023 年 1 月—12 月在广州中医药大学附属南海妇产儿童医院就诊的 ASD 合并睡眠障碍患儿为研究对象。所有患儿均由儿童康复科副主任医师以上的临床专业医师, 参照美国精神疾病诊断标准 (DSM-V) 对 ASD 的诊断标准^[4] 和儿童睡眠习惯问卷 (Children's Sleeping Habits Questionnaire, CSHQ)^[5] (一般将总得分 ≥ 41 分定义为存在睡眠障碍), 进行精准的临床诊断。纳入标准: 1) 符合诊断标准; 2) 家长对治疗知情同意; 3) 配合完成各项评估及治疗者; 4) 年龄 3~6 岁; 5) 无颅脑活动性病变者。排除标准: 1) 体内有金属植入者; 2) 伴视觉、听觉障碍者; 3) 伴心、肝、肾等重要脏器疾病者; 4) 未完成康复治疗, 中途退出。

共纳入 60 例患儿, 采用随机数表法分为研究组与对照组, 各 30 例。两组性别、年龄、病程等一般资料比较, 差异无统计学意义 ($P > 0.05$), 具有可比性。见表 1。本研究符合知情同意原则, 经广州中医药大学附属南海妇产儿童医院伦理委员会批准 (编号: 2022-01)。

1.2 方法

1.2.1 治疗方法 对照组仅接受应用行为分析 (applied behavior analysis, ABA) 训练、感觉统合治

表 1 治疗前研究组和对照组患儿性别、年龄、病程比较 ($\bar{x} \pm s$)

Tab. 1 Comparison of gender, age and course of disease between study group and control group before treatment ($\bar{x} \pm s$)

组别	例数	性别 (n)		入组年龄 (岁)	病程 (年)
		男	女		
研究组	30	25	5	4.32 $\pm$ 0.99	1.86 $\pm$ 0.58
对照组	30	24	6	4.62 $\pm$ 0.87	1.91 $\pm$ 0.63
χ^2/t 值		0.111 ^a		1.247 ^b	0.349 ^b
P 值		0.739		0.217	0.729

注: ^a χ^2 值, ^b t 值。

疗和言语治疗等常规教育康复训练, 研究组在对照组治疗项目基础上加超低频经颅磁刺激治疗。1) 超低频经颅磁刺激治疗: 采用 KF-10 型号的超低频经颅磁刺激仪。该治疗仪可选择各种神经递质对应的参数, 针对性地输入单个或组合特征频率的磁场。本研究组选用统一的治疗方案: γ -氨基丁酸 (gamma-aminobutyric acid, GABA), 治疗时间为 30 min。2) 常规康复训练包括应用行为分析法、感觉统合训练和言语治疗等, 训练方法以个体与集体训练相结合, 根据患儿的具体情况制定训练方案。每节训练时间 30 min。以上所有治疗均 1 次/d, 每周 5 d, 连续治疗 12 周。

1.2.2 观察指标

1.2.2.1 儿童睡眠习惯量表^[6] 儿童睡眠习惯量表 (Children's Sleep Habits Questionnaire, CHSQ) 是一项多维、家长报告的调查, 用于测量儿童睡眠模式和筛查睡眠问题, 共 45 个条目, 其中 33 条计分项目, 分为睡眠阻抗、睡眠焦虑、睡眠时间、异态睡眠、夜醒、睡眠呼吸、日间困倦、睡眠延迟等 8 个分问卷, 总分共 99 分, 即 33 条项目得分相加之和。一般将总得分 ≥ 41 分定义为存在睡眠障碍, 其总得分和各分问卷得分越高说明睡眠问题越严重。该量表信度和效度已被多项研究验证, Cronbach's α 系数为 0.7~0.8 之间, 重测信度组内相关系数在 0.62~0.79 之间。

1.2.2.2 孤独症评定量表^[7] 临床医生采用孤独症评定量表 (Child Autism Rating Scale, CARS) 观察和评估 ASD 儿童的语言、行为和感知觉等 15 项内容, 量表总分为 60 分, 得分 ≥ 30 分可诊断为 ASD, 得分越高越严重。该量表具有良好的信度和

效度,该量表 Cronbach's α 系数为 0.80~0.95 之间。
1.2.2.3 孤独症儿童行为量表^[7] 孤独症儿童行为量表 (Autism Behaviour Bheclist, ABC) 常用于 ASD 儿童的临床疗效评价,该量表可归纳为感觉、交往、躯体运动、语言、生活自理 5 个因子。ABC 量表的总分 158 分,筛查界线为 57 分,诊断分为 >67 分,得分越高越严重。该量表 Cronbach's α 系数为 0.80~0.95 之间。

以上所有评估均由临床医生分别在治疗前及治疗(12 周)后对患儿进行评估。

1.3 质量控制 对量表评估人员进行同质化培训,并建立单盲法评估体系,减少评估者选择性偏倚。数据采用双录入并对比以减少输入过程产生的误差,确保数据准确。

1.4 统计学方法 采用 SPSS 21.0 软件分析数据。正态分布的连续变量以 $\bar{x} \pm s$ 表示,两组之间比较采用 t 检验;非正态分布的连续变量以 $M(P_{25}, P_{75})$ 表

示,两组之间比较采用非参数检验。计数资料以例数(%)表示,两组之间比较采用 χ^2 检验。检验水准 $\alpha=0.05$ (双侧)。

2 结果

2.1 研究组与对照组患儿治疗前后睡眠障碍改善情况 研究组治疗后在 CSHQ 评分中睡眠阻抗、睡眠焦虑、睡眠时间、异态睡眠、日间困倦及总分得分较治疗前明显降低($P<0.05$),而夜醒、睡眠呼吸、睡眠延迟差异无统计学意义($P>0.05$),对照组治疗后 CSHQ 中各项分问卷指标及总分差异无统计学意义($P>0.05$)。见表 2。研究组在 CSHQ 评分中睡眠阻抗、睡眠焦虑、睡眠时间、异态睡眠、日间困倦及总分治疗前后得分的差值显著高于对照组($P<0.05$),而夜醒、睡眠呼吸、睡眠延迟两组之间的差值差异无统计学意义($P>0.05$)。见表 3。

表 2 研究组和对照组患儿治疗前后 CHSQ 各项目评分组内比较($\bar{x} \pm s$)

Tab. 2 Intra-group comparison of CHSQ scores before and after treatment in the study group and control group ($\bar{x} \pm s$)

项目	对照组($n=30$)				研究组($n=30$)			
	治疗前	治疗后	t 值	P 值	治疗前	治疗后	t 值	P 值
睡眠阻抗	8.53±2.85	7.83±2.59	0.996	0.324	8.40±1.79	7.27±1.80	2.438	0.018
睡眠焦虑	5.63±2.43	5.41±2.54	0.343	0.733	5.83±1.78	4.77±1.85	2.261	0.027
睡眠时间	5.50±2.10	5.38±1.81	0.237	0.813	4.83±1.32	4.03±1.38	2.295	0.025
异态睡眠	9.77±2.69	9.38±2.61	0.570	0.571	9.33±2.47	7.60±1.99	2.987	0.004
夜醒	4.53±1.46	4.31±1.18	0.642	0.523	4.10±1.27	3.83±1.21	0.843	0.403
睡眠呼吸	3.53±1.30	3.45±1.25	0.243	0.809	3.33±0.71	3.37±0.81	0.203	0.840
日间困倦	11.67±2.95	11.41±2.76	0.353	0.726	12.03±2.03	9.00±1.91	5.954	<0.001
睡眠延迟	1.83±0.75	1.79±0.71	0.212	0.833	1.90±0.80	1.70±0.75	0.999	0.322
CHSQ 总分	51.00±7.49	48.97±7.04	1.082	0.284	49.77±6.00	41.57±5.50	5.518	<0.001

表 3 研究组和对照组患儿治疗前后 CHSQ 各项目评分差值组间比较($\bar{x} \pm s$)

Tab. 3 Comparison of CHSQ difference scores before and after treatment between the study group and control group($\bar{x} \pm s$)

项目	治疗前后差值		t 值	P 值
	对照组($n=30$)	研究组($n=30$)		
睡眠阻抗	0.52±0.93	1.13±1.20	2.201	0.032
睡眠焦虑	0.24±0.63	1.07±1.95	2.218	0.030
睡眠时间	0.14±0.68	0.80±1.21	2.604	0.012
异态睡眠	0.41±0.81	1.73±2.02	3.322	0.002
夜醒	0.24±0.68	0.27±0.58	0.184	0.855
睡眠呼吸	0.10±0.31	-0.03±0.61	1.041	0.302
日间困倦	0.24±0.94	3.03±2.09	6.668	<0.001
睡眠延迟	0.03±0.56	0.20±0.54	1.197	0.236
CHSQ 总分	1.93±2.36	8.20±3.45	8.216	<0.001

2.2 研究组与对照组患儿治疗前后核心症状改善情况 研究组、对照组治疗后 CARS、ABC 总分均

较治疗前显著降低($P<0.05$)。见表 4。研究组 ABC 总分治疗前后的差值(11.80 ± 4.51)显著大于对照组(8.17 ± 4.50),差异有统计学意义($t=3.121, P=0.003$);而 CARS 总分的差值在研究组(2.33 ± 2.32)和对照组(2.67 ± 2.76)之间差异无统计学意义($P>0.05$)。

3 讨论

3.1 超低频经颅磁刺激治疗可改善 ASD 患儿睡眠障碍及核心症状 本研究表明,ILF-TMS 可以有效改善 ASD 患儿睡眠障碍,效果主要体现在患儿睡眠阻抗、睡眠焦虑、睡眠时间、异态睡眠、日间困倦方面,对照组则无明显改善。同时,研究组 CARS 总分及 ABC 总分较治疗前显著降低,且治疗前后 ABC 总分的差值较对照组差异有统计学意义,进一步说明超低频经颅磁刺激结合康复训练,可更有效促

表 4 研究组 and 对照组患儿治疗前后 CARS、ABC 总分组内比较($\bar{x} \pm s$)

Tab. 4 Intra-group comparison of CARS and ABC before and after treatment in the study group and control group($\bar{x} \pm s$)

项目	对照组($n=30$)				研究组($n=30$)			
	治疗前	治疗后	t 值	P 值	治疗前	治疗后	t 值	P 值
CARS 总分	36.63 $\pm$ 4.91	33.97 $\pm$ 4.91	2.098	0.040	34.30 $\pm$ 2.82	31.97 $\pm$ 3.06	3.067	0.003
ABC	73.93 $\pm$ 15.83	65.77 $\pm$ 14.32	2.094	0.041	73.07 $\pm$ 14.74	61.27 $\pm$ 14.51	3.125	0.003

进患儿核心症状的改善。

3.2 儿童 ASD 合并睡眠障碍的病因研究及相互影响 该病病因、病理机制复杂,至今尚未完全明确。近年来,研究指出其可能与神经生化因素、脑器质因素、遗传因素、免疫学因素等密切相关^[8-9],且大多患儿存在神经递质的异常,ASD 患儿睡眠障碍可能与多巴胺、谷氨酸、GABA 和 5-HT 等神经递质异常和褪黑素分泌不足有关^[10-12]。而睡眠障碍是 ASD 患儿最常见的共患病之一^[13-14],长期的睡眠障碍可能导致神经发育功能异常^[15-16]。Horiuchi 等^[17]研究发现,ASD 患儿更容易表现为睡眠抵抗、昼夜节律紊乱及中午以外的时间嗜睡。一项 1 784 例 ASD 患儿睡眠行为的调查显示,睡眠障碍与社交技能降低、攻击行为、焦虑、情绪变化、对环境变化敏感等显著相关^[18]。同时,越来越多的研究认为睡眠问题可能是 ASD 儿童症状加重的独立预测因素^[19],他们多存在睡眠-行为-精神相互作用,睡眠问题与其行为、认知功能、社交互动、情绪以及感觉敏感性密切相关^[20]。因此,改善睡眠问题对于提高 ASD 儿童临床疗效具有十分重要的意义。目前,临床治疗主要以行为干预、褪黑素等药物治疗及替代疗法为主,较少应用经颅磁刺激等物理疗法。本研究中,超低频经颅磁刺激结合康复训练,不仅改善了患儿睡眠障碍,且更有效地缓解了 ASD 临床症状。

3.3 超低频经颅磁刺激作用机制 ILF-TMS 属于一种新型的物理治疗方法,可据脑电超慢波频率、神经递质间的对应关系,通过磁场对患儿产生毫赫兹的感应电流,进而对各种递质的电活动产生调节作用,且不直接刺激神经细胞而产生动作电位,而将原动作电位的功效平衡、放大,有助于对脑组织的生理功能产生积极作用^[21-22]。机体大脑皮层网络的动态平衡状态主要由兴奋性锥体谷氨酸(glutamic acid, Glu)能神经元和抑制性 γ -氨基丁酸(γ -aminobutyric acid, GABA)能神经元共同维持。研究证实在 ASD 个体中,神经元的异常径向迁移导致了以前额叶皮质(prefrontal cortex, PFC)为主的局灶性大脑发育不良^[23],而在 ASD 个体尸检的大脑样本中,PFC 存在抑制性中间神经元数量的显著减少。此外,Fatemi 等^[24]关于 ASD 的尸检研究发现,

其大脑皮层和小脑中不仅存在 GABA 受体亚基的表达减少,而且参与合成 GABA 的酶也减少约 50%。事实上,GABA 是中枢神经系统中最主要的抑制性递质^[25],在促进“觉醒-睡眠”周期中发挥重要作用,可显著抑制中枢神经元兴奋^[26]。因此,抑制性 GABA 能的缺陷可能是 ASD 个体存在睡眠障碍、抑制不能、情绪控制不佳及感觉失调的原因。另外,徐建兰等^[27]通过采用连续 6 次 GABA 特征 ILF-TMS 刺激实验大鼠,大鼠脑内 GABA 的功率逐渐升高,其他递质的功率降低。根据这一机理,本研究中针对性选择能产生 GABA 的单个特征频率磁场作为刺激参数,通过调节抑制性神经递质的释放和代谢,激活相关脑区的功能链接,恢复大脑网络的正常功能,从而改善 ASD 患儿睡眠问题和核心症状。本研究证实,GABA 特征性重复超低频经颅磁刺激通过有效改善 GABA 能的缺陷,减轻 ASD 患儿睡眠阻抗、睡眠焦虑、异态睡眠、日间困倦等问题,延长睡眠时间。

3.4 研究的不足之处及未来的展望 本研究取得一定的临床效果,但仍存在局限性。首先,在本研究中,研究组在夜醒、睡眠呼吸、睡眠延迟方面改善不明显,考虑可能与缺乏足够的睡眠行为教育有关。睡眠行为教育可以帮助患儿建立良好的睡眠习惯和行为,降低对环境的敏感。国外研究提示睡眠行为教育与治疗是干预 ASD 患儿睡眠障碍的有效方法^[28-29]。石娜娜等^[30]研究表明低频重复经颅磁刺激联合睡眠行为教育治疗可有效改善患儿夜醒及睡眠延迟等问题,降低感觉敏感。因此,ILF-TMS 更应该与睡眠行为教育联合应用于 ASD 患儿的睡眠障碍。另外,本次研究样本量较小,研究时间较短,可能无法充分反映 ILF-TMS 治疗的总体效果及长期效果,研究组治疗前后 CARS 总分差值较治疗组并无显著差异。未来研究需进一步扩大样本量、延长研究时间,并积极开展 ILF-TMS 治疗与睡眠行为教育结合的临床研究,以更全面地评估 ILF-TMS 对 ASD 患儿治疗作用。

综上所述,ILF-TMS 作为一种新兴的非侵入性脑刺激技术,安全可靠,对改善 ASD 患儿睡眠障碍及核心症状具有显著作用,提高患儿及其家庭生活

质量。这为 ILF-TMS 在 ASD 患儿治疗中的应用提供了客观依据,具有广阔的应用前景。

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