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托吡酯联合左乙拉西坦对难治性癫痫患儿脑电活动、免疫球蛋白和生活质量的影响*

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摘要 目的：探讨托吡酯联合左乙拉西坦对难治性癫痫患儿脑电活动、免疫球蛋白和生活质量的影响。**方法：**选取2014年5月~2019年5月期间我院收治的80例难治性癫痫患儿，按照随机数字表法将患儿分为研究组(n=40)、对照组(n=40)，均予原抗癫痫药物治疗方案，并积极预防并发症，在此基础上，对照组患儿给予托吡酯治疗，研究组在对照组的基础上联合左乙拉西坦治疗，比较两组患儿疗效、脑电活动、免疫球蛋白水平、不良反应、生活质量。**结果：**研究组治疗3个月后的临床总有效率为90.00%(36/40)，高于对照组的70.00%(28/40)(*P*<0.05)。两组患儿治疗3个月后癫痫样放电量、α波、β波、θ 波、δ 波数量均下降，且研究组低于对照组(*P*<0.05)。两组患儿治疗3个月后免疫球蛋白A(IgA)、免疫球蛋白G(IgG)水平均升高，且研究组高于对照组(*P*<0.05)；两组患儿治疗3个月后免疫球蛋白M(IgM)水平未见显著变化，且组间比较无差异(*P*>0.05)。两组患儿治疗3个月后发作担忧、社会功能、情绪、精力等评分均升高，且研究组高于对照组(*P*<0.05)。两组不良反应发生率对比未见统计学差异(*P*>0.05)。**结论：**难治性癫痫患儿经托吡酯联合左乙拉西坦治疗后，患儿脑电活动得到有效控制，患儿免疫功能及生活质量均得到有效改善，用药安全性较好，具有一定的临床应用价值。

关键词：托吡酯；左乙拉西坦；难治性癫痫；脑电活动；免疫球蛋白；生活质量

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Effects of Topiramate Combined with Levetiracetam on EEG Activity, Immunoglobulin and Quality of Life in Children with Intractable Epilepsy*

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ABSTRACT Objective: To explore the clinical effect of topiramate combined with levetiracetam on EEG activity, immunoglobulin and quality of life in children with intractable epilepsy. **Methods:** 80 children with intractable epilepsy who were admitted to our hospital from May 2014 to may 2019 were selected, they were divided into study group (n=40), control group (n=40) according to the method of random number table. All patients were treated with the original antiepileptic drugs, and actively prevented complications, on the basis of them, Children in the control group were treated with topiramate, while those in the study group were treated with levetiracetam on the basis of the control group. The therapeutic effect, EEG activity, immunoglobulin level, adverse reactions and quality of life were compared between the two groups. **Results:** The total clinical effective rate of the study group was 90.00% (36/40), which was higher than 70.00% (28/40) of the control group (*P*<0.05). 3 months after treatment, the epileptiform discharge, α wave, β wave, θ wave and δ wave of the two groups were all decreased, and those of the study group were lower than those of the control group (*P*<0.05). The levels of immunoglobulin A (IgA) and immunoglobulin G (IgG) in the two groups increased at 3 months after treatment, and those of the study group were higher than those of the control group (*P*<0.05). There was no significant change in immunoglobulin M (IgM) in the two groups at 3 months after treatment, and there was no difference between the two groups (*P*>0.05). The scores of anxiety, social function, emotion and energy were all increased in the two groups at 3 months after treatment, and those of the study group were higher than those of 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:** After treatment with topiramate and levetiracetam, the EEG activity of children with intractable epilepsy is effectively controlled, the immune function and quality of life of children are effectively improved, and the drug safety is good, which has certain clinical application value.

Key words: Topiramate; Levetiracetam; Intractable epilepsy; EEG activity; Immunoglobulin; Quality of life

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前言

癫痫是多发于小儿的一类因神经元异常放电进而引起短暂性大脑功能失常的疾病[1]。难治性癫痫则是指癫痫患儿在应用常规的基础治疗后，仍未见明显好转的一类癫痫[2]。既往研究结果显示，小儿难治性癫痫发作症状复杂多样，若未能及时予以治疗，可造成小儿发育迟缓、智力低下，严重者甚至造成死亡[3]。现临床针对难治性癫痫患儿的药物治疗方案尚未完全统一，托吡酯是经美国神经学会（American Academy of Neurology，ANN）推荐的新型广谱抗癫痫药物，可用于治疗各类癫痫[4]，然而由于难治性癫痫发病机制极其复杂，单一的用药治疗并不能达到理想的治疗效果。左乙拉西坦最初于美国上市，是一种新型的抗癫痫药物，现已成为美国癫痫治疗中心的标准方案中药物之一[5]。本研究通过对我院收治的部分难治性癫痫患儿给予托吡酯联合左乙拉西坦治疗，疗效显著，现整理如下。

1 资料与方法

1.1 基线资料

选取 2014 年 5 月 ~2019 年 5 月期间我院收治的 80 例难治性癫痫患儿。纳入标准：（1）诊断标准参考《实用神经病学》[6]；（2）经影像学、症状学以及脑电图确诊；（3）患儿父母或监护人知情本次研究且签署了同意书；（4）经两种药物或两种治疗方法足量足疗程的治疗仍未得到有效控制；（5）年龄 6~14 岁。排除标准：（1）合并免疫缺陷、哮喘等影响免疫疾病者；（2）合并心肝肾等重要脏器功能障碍者；（3）合并急慢性感染者；（4）对本次研究用药存在禁忌症者；（5）患儿依从性差，中途退出治疗者。根据随机数字表法分为研究组（n=40）、对照组（n=40），其中对照组女 16 例，男 24 例，年龄 7~12 岁，平均（9.63±1.09）岁；病程 1~3 年，平均（2.32±0.43）年；癫痫类型：单纯部分性发作 12 例，部分继发全面性发作 15 例，复杂部分性发作 13 例。研究组女 15 例，男 25 例，年龄 6~14 岁，平均（9.58±1.16）岁；病程 0.8~3 年，平均（2.29±0.51）年；癫痫类型：单纯部分性发作 14 例，部分继发全面性发作 16 例，复杂部分性发作 10 例。两组一般资料比较无差异（P>0.05）。

1.2 方法

两组患儿治疗前行常规检查，给予二级护理。均予原抗癫痫药物治疗方案，在此基础上，对照组给予托吡酯（西安杨森制药有限公司，规格：25 mg，国药准字 H20020555）治疗，口服，起始剂量 0.5 ～1 mg/(kg·d)，随后每周增加 0.5～1 mg/(kg·d)，当剂量增加过程中，未见明显疗效增加的情况时，则以此剂量为维持剂量，目标剂量控制在 4~9 mg/(kg·d)。研究组在对照组的基础上联合左乙拉西坦（重庆圣华曦药业股份有限公司，规格：0.25 g，国药准字 H20163115）治疗，起始剂量以 10 mg/(kg·d)，口服，2 次 /d，随后每周增加 10 mg/(kg·d)，增至不发作或终剂量为 60 mg/(kg·d)。均连服 3 个月。

1.3 观察指标

（1）治疗 3 个月后，记录两组患儿临床疗效，疗效判定标准[7]如下：显效：治疗 3 个月后脑电图复查显示正常，临床症状消失，癫痫发作次数减少 >75%；有效：治疗 3 个月后临床症状、脑电图复查显示有所改善，癫痫发作次数减少 50%~75%；无效：未能达到上述标准者。总有效率 = 有效率 + 显效率。（2）于治疗前、治疗 3 个月后采用日本三荣公司生产的 EG-900 型九道脑电图机检测患儿脑电活动变化，单级、双级导联描记，计算患儿 20 min 内癫痫样放电量以及 30s 内的 α 波、β 波、θ 波、δ 波数量。（3）治疗前、治疗 3 个月后清晨抽取患儿空腹静脉血 4 mL。经离心半径 18 cm，4100 r/min 离心 12 min，分离待测。采用购自上海钰博生物科技有限公司的试剂盒，参考说明书操作，采用免疫比浊法检测免疫球蛋白 A（Immunoglobulin A，IgA）、免疫球蛋白 M（Immunoglobulin M，IgM）、免疫球蛋白 G（Immunoglobulin G，IgG）水平。（4）记录两组不良反应发生情况。（5）于治疗前、治疗 3 个月后采用癫痫患儿生活质量量表 -31（Quality of life scale for children with epilepsy-31，QOLIE-31）[8] 评估两组患儿生活质量。该量表包括社会功能、发作担忧、精力、情绪。各项评分 100 分，评分越高生活质量越好。

1.4 统计学方法

所有研究数据分析均采用 SPSS 25.0 统计学软件。计数资料以%表示，实施 χ^2 检验，计量资料以均值±标准差表示，实施 t 检验，检验标准设置为 α=0.05。

2 结果

2.1 临床疗效比较

治疗 3 个月后，研究组的临床总有效率为 90.00%（36/40），高于对照组的 70.00%（28/40）（P<0.05）；详见表 1。

表 1 临床疗效比较 例[（%）]

Table 1 Comparison of clinical effects n[（%）]

Groups	Markedly effective	Effective	Invalid	Total effective rate
Control group（n=40）	11（27.50）	17（42.50）	12（30.00）	28（70.00）
Study group（n=40）	15（37.50）	21（52.50）	4（10.00）	36（90.00）
χ^2				5.000
P				0.025

2.2 两组患儿脑电活动比较

两组患儿治疗前癫痫样放电量、α 波、β 波、θ 波、δ 波数量比较无差异（P>0.05）；两组患儿治疗 3 个月后癫痫样放电量、α 波、β 波、θ 波、δ 波数量均下降，且研究组低于对照组（P<0.05）；详见表 2。

2.3 免疫球蛋白比较

两组患儿治疗前 IgA、IgM、IgG 水平比较无差异（P>0.05）；两组患儿治疗 3 个月后 IgA、IgG 水平均升高，且研究组高于对

照组（P<0.05）；两组患儿治疗 3 个月后 IgM 水平未见显著变化，且组间比较无差异（P>0.05）；详见表 3。

表 2 两组脑电活动的比较（$\bar{x}\pm s$）

Table 2 Comparison of EEG activities between the two groups（$\bar{x}\pm s$）

Groups	Epileptiform discharge (n/20 min)		α wave(n/30s)		β wave(n/30s)		θ wave(n/30s)		δ wave(n/30s)	
	Before treatment	3 months after treatment	Before treatment	3 months after treatment	Before treatment	3 months after treatment	Before treatment	3 months after treatment	Before treatment	3 months after treatment
Control group (n=40)	22.46±3.11	15.41±2.18*	33.38±4.08	23.24±4.16*	23.58±4.14	17.67±3.24*	31.18±3.14	26.29±4.33*	26.84±2.99	21.44±2.29*
Study group (n=40)	22.59±2.46	9.55±2.28*	32.96±3.79	15.38±3.22*	23.63±4.17	11.35±3.38*	30.91±3.05	22.01±3.68*	26.91±3.01	17.83±2.96*
t	0.207	11.749	0.477	9.450	0.054	8.537	0.390	4.764	0.104	6.101
P	0.836	0.000	0.635	0.000	0.957	0.000	0.698	0.000	0.917	0.000

Note: Compared with before treatment, *P < 0.05.

表 3 两组免疫球蛋白的比较（$\bar{x}\pm s$，g/L）

Table 3 Comparison of immunoglobulins between the two groups（$\bar{x}\pm s$, g/L）

Groups	IgA		IgM		IgG	
	Before treatment	3 months after treatment	Before treatment	3 months after treatment	Before treatment	3 months after treatment
Control group (n=40)	0.59±0.07	0.81±0.09*	1.02±0.16	1.04±0.12	5.49±0.36	6.87±0.43*
Study group(n=40)	0.63±0.11	1.25±0.14*	1.06±0.11	1.07±0.16	5.54±0.31	8.45±0.51*
t	1.940	16.720	1.303	0.949	0.666	14.980
P	0.056	0.000	0.196	0.346	0.508	0.000

Note: compared with before treatment, *P < 0.05.

2.4 生活质量比较

两组患儿治疗前发作担忧、社会功能、情绪、精力的评分比较差异无统计学意义（P>0.05）；两组患儿治疗 3 个月后发作担忧、社会功能、情绪、精力的评分均升高，且研究组高于对照组（P<0.05）；详见表 4。

表 4 两组生活质量的比较（$\bar{x}\pm s$，分）

Table 4 Comparison of quality of life between the two groups（$\bar{x}\pm s$, scores）

Groups	Panic attack		Social function		Emotion		Energy	
	Before treatment	3 months after treatment	Before treatment	3 months after treatment	Before treatment	3 months after treatment	Before treatment	3 months after treatment
Control group (n=40)	55.82±6.23	64.53±7.28*	52.63±6.57	61.65±5.42*	55.92±6.52	63.52±7.21*	54.62±4.52	63.65±6.59*
Study group (n=40)	55.51±7.62	72.53±7.53*	52.82±5.32	70.01±6.34*	56.07±5.61	71.68±6.63*	54.59±5.68	69.52±7.54*
t	0.199	4.831	0.142	6.351	0.110	5.269	0.026	3.707
P	0.843	0.000	0.887	0.000	0.912	0.000	0.979	0.000

Note: Compared with before treatment, *P < 0.05.

2.5 不良反应比较

治疗期间，对照组出现头晕头痛 2 例、嗜睡 1 例、乏力 2 例；研究组出现头晕头痛 3 例、嗜睡 1 例、乏力 4 例；两组不良反应发生率对比无差异（χ^2=0.827，P=0.363）。

3 讨论

据以往报道统计，我国癫痫的患病率约为 7%，且多数在儿童期发病[9]。绝大部分癫痫患者经过常规的抗癫痫药物治疗，可获得良好的预后，而部分患者经抗癫痫药物足量足疗程治疗后仍无法得到有效控制，表现为癫痫长期的反复发作，最后发展为难治性癫痫[10]。现临床有关难治性癫痫的发病机制尚不十分明确，不少学者认为可能与异位神经元中各种受体的表达差

异和大脑皮质解剖学结构的不完整有关[11-13]。目前治疗难治性癫痫的方案众多，包括手术、物理、心理及药物治疗等，其中手术创伤大，患者多较为排斥，而物理、心理多因患儿自我管理能力较差，开展难度相对较大，药物治疗无疑成为最简便有效的一种治疗方式[14-16]。托吡酯是一种单糖基右旋果糖硫代物，既往常用于治疗癫痫、偏头痛、肥胖及精神障碍等病症[17,18]。但仍有部分难治性癫痫患儿对药物治疗反应不佳，病情持续进展。左乙拉西坦临床上主要用于成年人及四岁以上儿童癫痫患者部分发作的加强治疗，可有效缓解癫痫症状[19]。

本次研究结果中研究组治疗后的生活质量评分及临床疗效均优于对照组，可见托吡酯联合左乙拉西坦治疗难治性癫痫患儿，可进一步提高治疗效果，改善患儿生活质量。分析其原因，托吡酯治疗癫痫的作用机制主要在于以下几点：可有效阻断电压依赖性钠通道，进而缩短痫样放电持续时间，减少异常放电发生次数；通过拮抗 α- 氨基 -3- 羟基 -5- 甲基 -4- 异恶唑丙酸受体进而抑制大脑海马、皮质及交感神经元等细胞的钙内流；可增强氨基丁酸对神经的抑制作用，同时可抑制神经兴奋性，从而发挥保护神经元的作用[20-22]，而左乙拉西坦可通过与中枢神经的突触囊泡蛋白 2A 结合，进而调控突触囊泡内的神经递质释放，阻断神经元的异常放电[23,24]，两种药物发挥协同作用，产生良好的抗癫痫效果，症状得到明显改善后，患者心理压力得到缓解，自信心树立，因此生活质量亦相应提高。既往文献[25]报道，癫痫发作时神经元异常放电造成神经内分泌紊乱，进而引起免疫功能低下。免疫球蛋白如 IgA、IgG、IgM 是人体免疫系统的重要组成成分，主要通过特异性抗原结合及排除外来抗原进而发挥免疫作用[26,27]。本研究中托吡酯联合左乙拉西坦治疗患儿的免疫球蛋白改善情况均优于单用托吡酯治疗者，这可能是由于联合用药可更好的控制患儿癫痫，加强抵御外援微生物侵入能力，从而纠正免疫功能紊乱[28]。由于癫痫发作的主要特征为大脑异常放电，故脑电活动是否恢复正常也可用于判断癫痫治疗的疗效 [29]。本研究中两组患儿脑电活动均有所下降，且托吡酯联合左乙拉西坦治疗者改善效果更佳，这可能是因为左乙拉西坦经口服后生物利用度极佳，可被人体完全吸收，可辅助托吡酯发挥较好的改善患儿脑电活动作用[30]。另两组不良反应发生率对比无差异，可见安全性较好。

综上所述，采用托吡酯联合左乙拉西坦治疗可有效控制难治性癫痫患儿脑电活动，改善其免疫功能及生活质量，用药安全性较好，具有一定的临床应用价值。

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