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Original Article

Comparison of the Therapeutic Effects of Sodium Valproate and Levetiracetam on Pediatric Epilepsy and the Effects of Nerve Growth Factor and γ-Aminobutyric Acid

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Abstract

Background: We aimed to investigate the therapeutic effect of sodium valproate combined with levetiracetam on pediatric epilepsy and the effects of nerve growth factor and γ-aminobutyric acid.

Methods: Eighty-three epileptic children admitted to Xuzhou Municipal Hospital of Xuzhou Medical University (Xuzhou, China) from Jan 2018 to Nov 2019 were collected and divided into a control group (40 cases, treated with sodium valproate alone) and an observation group (43 cases, treated with sodium valproate combined with levetiracetam). The therapeutic effect and incidence of adverse reactions were observed. The levels of nerve growth factor (NGF), γ-aminobutyric acid (GABA) and serum neuron-specific enolase (NSE) of children were compared. Changes of cognitive function and the total effective rate were evaluated. Logistic regression analysis was used to analyze the risk factors affecting the therapeutic effect.

Results: After treatment, NGF, GABA and NSE in the observation group were significantly improved compared with those before treatment. The cognitive function of the observation group was significantly improved after treatment when compared with the control group. The total effective rate in the observation group was higher than that in the control group. Adverse reactions in the observation group were less than those in the control group. Seizure type, NGF, GABA, NSE and treatment methods were independent risk factors affecting the therapeutic effect of pediatric epilepsy.

Conclusion: The application of sodium valproate combined with levetiracetam in the treatment of pediatric epilepsy is helpful to improve the overall therapeutic effect, significantly improve the cognitive function of children, and improve the levels of NGF, GABA and NSE.

Keywords: Pediatric epilepsy; Sodium valproate; Levetiracetam; Nerve growth factor; γ-aminobutyric acid

Introduction

Epilepsy is a neurological disease with an incidence second only to stroke (1). The etiology of the disease is relatively complex, including internal and external factors of main organisms, internal factors such as congenital abnormalities of

central nervous system, and external factors such as craniocerebral trauma and brain tumor (2).

The genetic tendency of the disease is obvious, and the incidence rate of males is generally higher than that of females (3). At the same time, a study found a strong correlation with the patient's age, especially the high incidence rate among children (4). As the brain and whole body organs of the affected children are immature and in their development period, pediatric epilepsy is extremely easy to damage neurons of them, induce cerebral apoplexy, anoxia and other diseases in children, and in serious cases, mental retardation will occur, which brings great damage to children's body and mind and also increase the burden on parents and society (5). Pediatric epilepsy is a convulsive seizure caused by paroxysmal and temporary brain dysfunction (6).

Currently, anti-epileptic drugs are mainly selected clinically to treat pediatric epilepsy (7). Due to the large side effects, poor therapeutic effect and poor compliance of single antiepileptic drugs, repeated seizures of pediatric epilepsy are caused. Therefore, exploring safe and effective treatment has become the primary clinical task (8). Its symptom group is mostly transient and simple partial facial hemimotor seizure, such as transient tonic or clonic twitch of unilateral facial muscle, oropharyngeal muscle and oral lip (9).

At present, there is no unified standard for clinical treatment of pediatric epilepsy (10). Most medical workers choose first-line antiepileptic drugs such as sodium valproate, carbamazepine, lamotrigine, gabapentin, oxcarbazepine, phenytoin and levetiracetam for treatment (11). Sodium valproate, as a widely used broad-spectrum antiepileptic drug in clinic, is mainly applied to control the concentration of inhibitory nerve medium γ-aminobutyric acid (GABA) in the brain of epileptic children to produce antiepileptic effect (12). Levetiracetam is a new clinical oral antiepileptic drug, which is different from the structure of other antiepileptic drugs and has a brand-new antiepileptic mechanism, but its exact mechanism of action is still unclear (13).

As the first discovered neurotrophic factor, nerve growth factor (NGF) plays an important role in brain and neuron development and maintenance of balance. γ-aminobutyric acid (GABA) is a major inhibitory neurotransmitter existing in the central nervous system. GABA is related to various nervous system diseases such as anxiety, depression, and schizophrenia, which participates in more than 40% of inhibitory nerve conduction. Serum neuron-specific enolase (NSE) is a key enzyme in cell energy metabolism. It is mainly involved in glycolysis process. It is a specific protein existing in cytoplasm, mostly appearing in the form of dimer, distributed in neuroendocrine cells and neuron cells, with very little content in blood and cerebrospinal fluid. It is sometimes difficult to control the disease condition with single clinical medication (14). The therapeutic effect is not high, prone to adverse reactions, side effects, etc., and the therapeutic effect is not ideal (15). How to reduce the pain of epileptic children to the greatest extent and improve the therapeutic effect and quality of life is the goal pursued by clinical treatment (16).

At present, the combination therapy is a clinically better treatment scheme (17), however, the study on the medication scheme of sodium valproate combined with levetiracetam is relatively few. Therefore, this study compares the therapeutic effect of sodium valproate alone and combined with levetiracetam in the treatment of pediatric epilepsy, and its influence on NGF, GABA and NSE, to evaluate the therapeutic effect of the two drug regimentation in the treatment of epilepsy, hoping to provide new ideas and clinical reference value for the clinical treatment of epilepsy.

Methods

General Data

Overall, 83 epileptic children admitted to Xuzhou Municipal Hospital of Xuzhou Medical University (Xuzhou, China)from Jan 2018 to Nov 2019 were selected and divided into an observation group and a control group. Inclusion criteria: All subjects were diagnosed as epilepsy according to the diagnostic criteria of the International League against Epilepsy (ILAE) (18). Children in both

groups did not receive any antiepileptic drugs before admission. No abnormality was found in MRI and CT examination of the head of children. Children with normal development. Exclusion criteria: Children with severe mental illness and psychosis. Children with other serious diseases. Children with allergic constitution. Children withdrew from the research halfway or lost to follow-up.

This study has been approved by the Ethics Committee of *Xuzhou* Municipal Hospital of Xuzhou Medical University. All children and their families have been informed and signed a fully informed consent form.

Treatment methods

Children in the control group were treated with sodium valproate alone [Sanofi, Hangzhou, China, H20010595]. The children were given a dose of 15 mg/(kgd) for the first time (19), divided into 2-3 times of oral administration, gradually increased by 5-10 mg/kg every week until 30-40 mg/kg, and then continued to be treated according to this dose. The children in the observation group were treated with levetiracetam [Youshibi (Zhuhai) Pharmaceutical Co., Ltd., Zhuhai, China, J20150004] on this basis of the control group. The first dose was 20 mg/(kgd) (6), divided into two oral doses, gradually increased by about 5-10 mg/kg every week until the dose reached 30-40 mg/kg, and then continued to be treated according to this dose. All subjects were treated continuously for 4 months.

Outcome measures

Before and after treatment, liver function, renal function and blood routine were examined for all epileptic children, and adverse reactions were observed. The levels of NGF, GABA and NSE in serum of children in both groups before and after treatment were detected by enzyme-linked immunosorbent assay (ELISA) kits (20). The kits were purchased from Shanghai Jingkang Bioengineering Co., Ltd., Shanghai, China, JK-(a)-1690, JK-EA00278 and JK-EA00252, respectively. The overall therapeutic effect of the two groups of children, including frequency of seizures, duration of seizures, and degree of EEG changes. Wechsler Intelligence Scale for Children (WISC-CR) was used to evaluate the cognitive function of the two groups of children before and after treatment (21). It mainly includes two parts: speech scale and operation scale. The speech scale consists of five sub-tests of information, similarities, arithmetic, vocabulary and comprehension. The operation scale consists of five subtests of mapping, arrangement, building blocks, puzzles and decoding. All children were evaluated by the same professional staff. All scales were counted first, and then converted into verbal intelligence quotient (VIQ), performance intelligence quotient (PIQ) and full-scale intelligence quotient (FIQ). The higher the score was, the better the cognitive function of epileptic children was (22).

Criteria of therapeutic effect judgment

It was evaluated according to the control degree of epileptic seizure frequency in epileptic children. Basic cured: Epilepsy completely controlled, no seizure, epileptiform discharge completely disappeared. Markedly effective: Epileptic seizure frequency reduced by more than 75%, epileptic discharge reduced by more than 50%. Effective: Epileptic seizure frequency reduced by 50% to 75%, epileptic discharge reduced by 25% to 49%. Ineffective: epileptic seizure frequency reduced below 50%, epileptic discharge reduced below 25%. Total effective rate = (number of basic cured cases + number of markedly effective cases + number of effective cases) / total number of cases × 100%.

Statistical methods

SPSS ver.23.0 (Beijing EasyBio Co., Ltd., China) was used to carry out statistical analysis on the research data. Counting data were expressed by the number of cases / percentage (n/%), and chi-square test was used for comparison of counting data between groups. Measurement data were expressed by $\bar{x}\pm sd$. Independent sample t test was used for comparison of measurement data

between groups, and paired t-test was used for comparison before and after treatment in groups. One-way analysis of variance was used for data of more than two groups, and Bonferroni was used for pairwise comparison between groups. Logistics multivariate regression analysis was used to analyze the risk factors affecting the treatment effect of children. When $P<0.05$, the difference was statistically significant.

Results

Comparison of general data

There was no significant difference between the two groups in terms of gender, age, seizure type, course of disease, weight, family history of epilepsy, production mode, place of residence, parental smoking history, parental drinking history and other clinical baseline data (Table 1).

Table 1: Comparison of general data between the two groups [n(%)] ($\bar{x}\pm sd$)

Classification	*Observation group (n=43)*	*Control group (n=40)*	*t/χ^2 value*	P-*value*
Gender			0.053	0.819
Male	28 (65.12)	27 (67.50)		
Female	15 (34.88)	13 (32.50)		
Age (years)	8.82±7.63	8.52±7.84	0.177	0.860
Seizure type			0.019	0.999
Tonic-clonic seizure	15 (34.88)	14 (35.00)		
Simple partial seizure	10 (23.26)	9 (22.50)		
Complex partial seizure	13 (30.23)	12 (30.00)		
Secondary generalized seizure	5 (11.63)	5 (12.50)		
Course of disease (year)	1.3±0.4	1.4±0.6	0.899	0.371
Weight (kg)	15.52±8.02	14.98±7.98	0.307	0.759
Family history of epilepsy			0.029	0.863
With	18 (41.86)	16 (40.00)		
Without	25 (58.14)	24 (60.00)		
Production mode			0.232	0.630
Eutocia	28 (65.12)	24 (60.00)		
Caesarean	15 (34.88)	16 (40.00)		
Place of residence			0.075	0.784
Countryside	30 (69.77)	29 (72.50)		
City	13 (30.23)	11 (27.50)		
Parental smoking history			0.297	0.585
With	23 (53.49)	19 (47.50)		
Without	20 (46.51)	21 (52.50)		
Parental drinking history			0.003	0.953
With	25 (58.14)	23 (57.50)		
Without	18 (41.86)	17 (42.50)		

Comparison of therapeutic effect

After treatment, the total effective rate of the observation group was 95.35%, and that of the control group was 75.00%. In the observation group was higher than that of the control group (P<0.05) (Table 2).

Comparison of routine indexes between the two groups

There was no significant difference in liver function, renal function and blood routine between the two groups before and after treatment (Table 3).

Table 2: Therapeutic effect of children in two groups after treatment [n(%)]

Group	n	Clinical cured	Markedly effective	Effective	Ineffective	Total effective rate %
Observation group	43	20(46.51)	18(41.86)	3(6.98)	2(4.65)	41(95.35)
Control group	40	11(27.50)	16(40.00)	3(7.50)	10(25.00)	30(75.00)
χ^2	-	-	-	-	-	6.938
P	-	-	-	-	-	<0.05

Table 3: Comparison of routine indexes before and after treatment between two groups of children ($\bar{x}\pm sd$)

Group	WBC($\times10^9$) /L		RBC ($\times10^{12}$) /L		BUN (mmol/L)		Scr (μmol /L)		Upro (g /24h)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group (n=43)	7.55±2.11	7.49±2.48	4.46±0.31	4.39±0.21	8.01±1.34	8.04±1.38	80.17±10.27	79.87±9.56	6.85±2.34	6.76±1.45
Control group (n=40)	7.54±2.09	7.23±2.71	4.42±0.32	4.34±0.36	8.04±1.41	7.95±1.51	80.41±10.34	80.27±9.74	6.82±2.21	6.72±1.53
t	0.022	0.456	0.578	0.779	0.099	0.284	0.106	0.188	0.059	0.122
P	0.983	0.649	0.565	0.438	0.921	0.777	0.916	0.851	0.952	0.903

Comparison of NSE, NGF and GABA between the two groups

Before treatment, NSE, NGF and GABA levels of the two groups of children were compared, and there was no significant difference. After treatment, NSE and NGF levels in both groups decreased, and GABA levels increased. After treatment, compared with the control group, NSE and NGF levels in the observation group decreased more significantly, and GABA levels increased more significantly (Fig. 1).

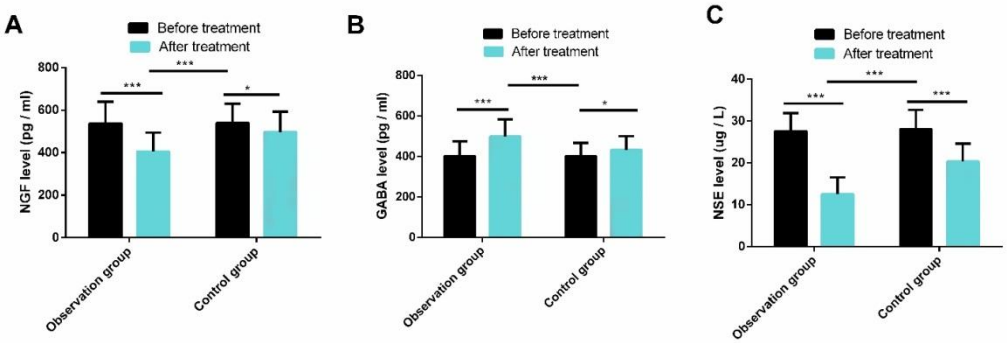

Fig. 1: Comparison of NSE, NGF, and GABA between the two groups

A) Comparison of NGF levels before and after treatment between the two groups. B) Comparison of GABA levels before and after treatment between the two groups. C) Comparison of NSE levels before and after treatment between the two groups.

Note: * P < 0.05, *** P < 0.001

Comparison of cognitive function between the two groups before and after treatment

Before treatment, there was no significant difference in cognitive function between the two groups. After treatment, the VIQ, PIQ and FIQ of the children in the control group had no obvious changes. Three children in the observation group were improved, and the three in the observation group were also significantly higher than those of the control group after treatment (Fig. 2).

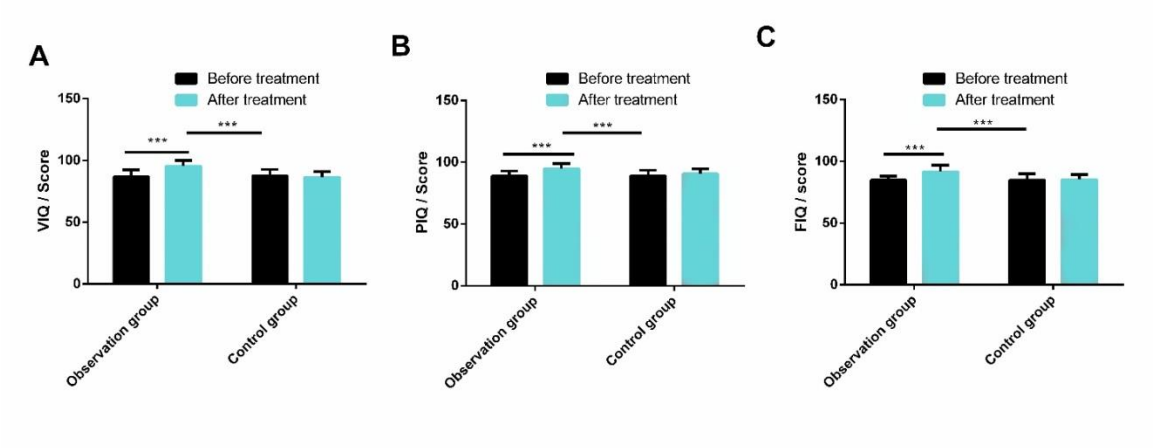

Fig. 2: Comparison of cognitive function between the two groups before and after treatment
A) Comparison of VIQ results before and after treatment between the two groups. B) Comparison of PIQ results between the two groups before and after treatment. C) Comparison of FIQ levels before and after treatment between the two groups.
Note: *** P<0.001

Comparison of adverse reactions

During the treatment, there were 4 cases of drowsiness, 4 cases of nausea and vomiting, 3 cases of dizziness and 2 cases of diarrhea in the control group, with an incidence of adverse reactions of 32.50%. There were 2 cases of diarrhea and 2 cases of dizziness in the observation group, with an incidence rate of adverse reactions of 9.30%. There was a significant difference between the two groups (P<0.05) (Table 4).

Table 4: Comparison of adverse reactions between the two groups [N (%)]

Group	*n*	*Dizziness*	*Nausea and vomiting*	*Diarrhea*	*Drowsiness*	*Total incidence rate*
Observation group	43	2(4.65)	0(0.00)	2(4.65)	0(0.00)	4(9.30)
Control group	40	3(7.50)	4(10.00)	2(5.00)	4(10.00)	13(32.50)
χ^2	-	-	-	-	-	6.847
P	-	-	-	-	-	<0.05

Logistic regression analysis on factors affecting the therapeutic effect of children

This study compared the differences between clinical parameters and related indexes between children with effective and ineffective treatment. There were 71 children with effective treatment and 12 children with ineffective treatment. There were no significant differences in age, gender, course of disease, weight, family history of epi-

lepsy, production mode, parental smoking history, parental drinking history and place of residenc, while there were statistical differences in seizure type, NGF, GABA, NSE and treatment methods (P<0.05). Finally, we analyzed the different factors by multivariate Logistic regression. Seizure type (P=0.013), NGF (P=0.010), GABA (P=0.012), NSE (P=0.016) and treatment methods (P=0.007) were independent risk factors affecting the treatment effect of epileptic children (Tables 5-7).

Table 5: Univariate analysis of poor prognosis in children with epilepsy [n(%) , $\bar{x}\pm sd$]

Factors	*n*	*Effective group (n=71)*	*Ineffective group (n=12)*	χ^2/t	P
Gender				0.001	0.971
Male	55	45(81.82)	10(18.18)		
Female	28	23(82.14)	5(17.86)		
Age (yr)				0.013	0.989
	83	8.72±7.33	8.69±7.44		
Course of disease (year)				1.061	0.318
	83	1.2±0.3	1.3±0.4		
Weight (kg)				0.055	0.956
	83	15.32±8.12	15.18±8.08		
Family history of epilepsy				0.003	0.957
With	34	29(85.29)	5(14.71)		
Without	49	42(85.71)	7(14.29)		
Production mode				0.111	0.738
Eutocia	52	45(86.54)	7(13.46)		
Caesarean	31	26(83.87)	5(16.13)		
Seizure type				6.200	0.013
Focal seizure	48	45(93.75)	3(6.25)		
A generalized attack	35	26(74.29)	9(25.71)		
Parental smoking history				0.002	0.964
With	41	35(85.37)	6(14.63)		
Without	42	36(85.71)	6(14.29)		
Parental drinking history				0.449	0.503
With	48	40(83.33)	8(16.67)		
Without	35	31(88.57)	4(11.43)		
Place of residence				0.105	0.746
Countryside	59	50(84.75)	9(15.25)		
City	24	21(87.50)	3(12.50)		
NGF (pg/ml)				5.166	< 0.001
	83	400.16±86.56	540.81±91.37		
GABA (pg/ml)				2.442	0.016
	83	462.37±83.23	400.44±67.31		
NSE (ug/L)				12.60	< 0.001
	83	13.53±3.68	28.62±4.72		
Treatment methods				6.938	< 0.001
Sodium valproate therapy	40	30(75.00)	10(25.00)		
Treatment of Sodium Valproate Combined with Levetiracetam	43	41(95.35)	2(4.65)		

Table 6: Logistic multivariate regression analysis assignment

Factors	*Variable*	*Assignment*
Seizure type	X1	Focal attack = 0, generalized attack = 1
NGF(pg/ml)	X2	The data belongs to the continuous variables and is analyzed with the original data
GABA(pg/ml)	X3	The data belongs to the continuous variables and is analyzed with the original data
NSE(ug/L)	X4	The data belongs to the continuous variables and is analyzed with the original data
Treatment methods	X5	Sodium valproate treatment = 0, sodium valproate combined with levetiracetam treatment = 1

Table 7: Multivariate logistic regression analysis on effect of pediatric epilepsy

Variable	*B*	*S.E*	*Wals*	P	*OR*	*95% CI*
Seizure type	1.334	0.372	5.438	0.013	2.341	1.241~6.122
NGF(pg/ml)	1.538	0.808	9.985	0.010	3.212	1.615~6.430
GABA(pg/ml)	1.361	0.587	4.968	0.012	3.181	1.581~6.262
NSE(ug/L)	1.239	0.597	5.223	0.016	3.194	1.587~6.488
Treatment methods	2.445	0.988	5.328	0.007	5.413	2.717~10.876

Discussion

Pediatric epilepsy can cause brain tissue development disorder, damage the nervous system, and eventually lead to mental disorders. It will have different degrees of negative effects on its neurocognitive and psychological aspects. At present, the treatment of pediatric epilepsy is mainly drug therapy (23). The treatment of pediatric epilepsy mainly lies in relieving or even eliminating the clinical symptoms of epileptic children and controlling the seizure frequency. Due to the younger age of children, their resistance is weak and drug resistance is poor, the safety and effectiveness of the selected treatment scheme are extremely important (24).

Sodium valproate, one of the most commonly used antiepileptic drugs in the clinic, is a broad-spectrum drug with high selectivity (25). Its main mechanism of action is to increase the concentration of GABA, effectively enhance its postsynaptic response, strengthen the inhibition of neuronal activity, and control the occurrence of epilepsy (26). Sodium valproate, as a single drug, is sometimes difficult to completely control the disease (27). Levetiracetam is one of the most promising antiepileptic drugs clinically at this stage. It has the advantages of fast absorption, high bioavailability, rapid onset of action and easy tolerance (28). The mechanism of levetiracetam in anti-epilepsy is quite different from that of sodium valproate. The drug has no significant effect on GABA neurotransmitter and glycine in epileptic children. Through the direct effect on the synaptic vesicle protein 2 (SV2) in the central nerve of children with epilepsy, it can effectively inhibit the abnormal discharge of children with epilepsy, to promote the normal release of neurotransmitters in the brain. At the same time, levetiracetam also has the effect of reducing CAI hippocampal activity and forming an effective N-type calcium channel through inhibiting brain hippocampal activity of epileptic children. When GABA is placed on the hippocampus of the child, it not only enhances the inhibitory effect on central nervous system but also effectively protects neurons of epileptic children (29). Sodium valproate was combined with levetiracetam can significantly improve the therapeutic effect in the treatment of pediatric epilepsy. In this study, the total effective rate of the observation group was 95.35%,

and that of the control group was 75.00%. The overall therapeutic effect of the observation group was remarkably better than that of the control group, indicating that the combination of sodium valproate and levetiracetam can improve the effective rate of treatment (30). Levetiracetam not only plays a significant role in controlling epileptic seizures, but also can improve the cognitive function of epileptic children, thus improving their quality of life.

The results of this study showed that the improvement of cognitive function in the observation group was notably better than that in the control group after treatment, indicating that levetiracetam can improve cognitive function in clinical treatment. In addition, levetiracetam is less bound to plasma proteins in the treatment of pediatric epilepsy, and is not metabolized through the children's liver, but effectively eliminated by the children's kidney, thus greatly reducing the damage of drugs to the liver (31). In this study, the incidence of adverse reactions in the observation group was remarkably lower than that in the control group, indicating that levetiracetam has fewer side effects in the treatment of pediatric epilepsy. At last, we analyzed the risk factors. Seizure types, NGF, GABA, NSE and treatment methods were independent risk factors affecting the therapeutic effect of pediatric epilepsy. NGF, GABA and NSE are the main risk factors for pediatric epilepsy (32).

NGF is an important nutrient substance in the nervous system that can promote the growth of nerve synapses. NGF produces a marked effect on the development of brain and neurons and the maintenance of balance (33). NGF has dual biological functions. On the one hand, it can promote the recovery of neurons and reduce the apoptosis rate of neuron cells, thus inhibiting epileptic activities. On the other hand, its expression is notably up-regulated during epileptic seizures, which can affect the function of nerve cells, interfere with brain excitation, and lead to the occurrence and progress of epilepsy (34). Epilepsy cannot develop without the imbalance between arousal and inhibition in the brain (35). When the balance is broken, the content of excitatory amino acid transmitter in the brain increases and the content of inhibitory amino acid transmitter decreases. GABA is the main inhibitory amino acid transmitter, it can release inhibitory transmitter GABA in numerous regions of the brain. By mediating inhibitory synaptic transmission, abnormal discharge of brain neurons can be prevented and the main inhibitory effect can be exerted. NSE is mainly produced in neuroendocrine cells and participates in the metabolism of nerve cells. In normal organisms, its detection rate is extremely low (36). For epilepsy patients, due to nerve cell damage, a large amount of NSE in cells is released into cerebrospinal fluid, which increases its content. Therefore, NSE level is related to the degree of nerve cell damage, so the degree of brain injury can be evaluated by detecting the level (36).

Our results showed that NGF and NSE levels decreased in both groups decreased after treatment, and the degree of decrease in the observation group was more remarkable. GABA levels all increased, which was more significant in the observation group. These indicate that the combination of sodium valproate and levetiracetam can reduce the level of NGF and improve the level of GABA.

Conclusion

The combined application of levetiracetam and sodium valproate in the treatment of pediatric epilepsy can remarkably improve the therapeutic effect, inhibit the levels of NGF and NSE, and enhance the inhibitory effect of GABA. At the same time, it is helpful to improve the cognitive function of children. The combined drug therapy scheme is worthy of clinical application and promotion. However, there is still room for improvement in this study. For example, the results of the study need to be verified by further expanding the sample size. The safety of these two treatment options and the mechanism of adverse reactions can be monitored. It is also possible to evaluate the therapeutic effect of the treatment scheme from more inflammatory cytokines.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Competing interest

The authors declare that there is no conflict of interest.

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