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Article

Levetiracetam plus Oxcarbazepine Combination Treatment Downregulates Serum Multidrug Resistance Protein 1 Levels and Upregulates Neuropeptide Y Levels in Children with Epilepsy

Jiahong Wang[1*]

[1]Department of Pediatrics, the Affiliated People's Hospital of Ningbo University, Ningbo City, Zhejiang Province, 315100, China

The aim of the present study was to investigate the usefulness of multidrug resistance protein 1 (MDR1) and neuropeptide Y (NPY) levels in predicting the efficacy of levetiracetam (LEV) plus oxcarbazepine (OXC) treatment administered to children with epilepsy and to determine their prognosis. Overall, 193 children with epilepsy admitted to the hospital were enrolled and randomly divided into two groups according to different treatment methods: group A (n = 106, treated with LEV plus OXC combination) and group B (n = 87, treated with OXC only). After treatment, compared with group B, group A exhibited a remarkably higher total effective rate and a significantly lower total adverse reaction rate. Areas under the curve for MDR1 and NPY for predicting ineffective treatment were 0.867 and 0.834, whereas those for predicting epilepsy recurrence were 0.916 and 0.829, respectively. Electroencephalography abnormalities, intracranial hemorrhage, neonatal convulsion, premature delivery, and MDR1 and NPY levels were independent risk factors for poor prognosis in children with epilepsy. Serum MDR1 and NPY levels exhibited a high predictive value for early epilepsy diagnosis, treatment efficacy assessment, and prognostication in children with epilepsy treated with LEV plus OXC combination.

Keywords: Levetiracetam. Oxcarbazepine. Children with epilepsy. Multidrug resistance protein 1. Neuropeptide Y. Efficacy.

INTRODUCTION

Epilepsy predominantly occurs in infants and children (Thijs *et al.,* 2019), particularly in preschool children aged <5 years, and also there is a second peak coming with aging (Koop, Loman, 2017). Epilepsy is characterized by recurrent seizures that occur/attack without any known reason. Although there are numerous causes of epilepsy in children, the underlying pathogenesis remains unclear in most cases. Children with refractory epilepsy most often experience primary generalized seizures that are not amenable to surgery. By contrast, refractory epilepsy in adults is mostly focal in origin and the focus may be surgically accessible.

At present, drugs therapy is the main treatment option for epilepsy; however, most patients are resistant to it (Moshé *et al*., 2015). Therefore, there is an urgent need for novel effective methods. Levetiracetam (LEV)—a novel antiepileptic drug (AED) (Loiacono *et al*., 2016)—binds to synaptic vesicle protein 2A, thereby inhibiting calcium and neurotransmitter release in nerves (Gujjar *et al.,* 2017). It reportedly has high efficacy and safety (Weijenberg, Brouwer, Callenbach, 2015). Oxcarbazepine (OXC) is a first-line oral drug that exhibits excellent pharmacokinetic characteristics and has minimal interactions with other drugs (E and H, 2015). This oral drug is available for partial epilepsy treatment in adults and children (Lin *et al*., 2019). It

***Correspondence:** J. Wang. Department of Pediatrics. The Affiliated People's Hospital of Ningbo University. No.251, Baizhang East Road, Ningbo City, Zhejiang Province, 315100, China. Phone: +86-15869597957. Email: weixiaothr@163.com. ORCID: https://orcid.org/0000-0002-6078-3575

functions by blocking voltage-gated sodium channels in excitatory glutamatergic neurons, stabilizing overexcited neuron membranes, and inhibiting repeated neural discharge.

OXC regulates potassium and calcium activities and decreases glutamatergic transmission (Rodrigues *et al.*, 2017). Wang *et al.* stated that LEV plus OXC combination is effective in treating epilepsy in children as well as improves recognition function, thereby rendering it worthy of clinical popularization and application (Wang, Liang, 2017). In patients with cancer, multidrug resistance (MDR) has been a major obstacle that hinders their complete treatment (Chen *et al.*, 2016). MDR occurs in several tissues (such as the liver, placenta, and intestine) and can play a protective role by reducing the accumulation of exogenous molecules in sensitive organs or cells (Bossennec *et al.*, 2018). Studies have shown that epileptic seizures are closely related to the upregulated expression levels of the *MDR1* gene (Yang *et al.*, 2015). Neuropeptide Y (NPY)—an endogenous neuropeptide widely expressed in the central nervous system—is involved in various neural processes and neuropsychiatric disorders, such as anxiety disorders and fear of learning (Corder *et al.*, 2020).

A study has shown that NPY can selectively bind to neural cell adhesion molecules, induce neuroplasticity and neuroprotection, and act as a neurogenic agent for the treatment of pathological conditions (Woldbye *et al.*, 2018). NPY is one of the most investigated neuropeptides related to epilepsy. During seizures, NPY is highly upregulated, and its release is increased in epileptic regions (Ge *et al.*, 2017). The aim of this study was to determine NPY levels that could be possible biomarkers of drug efficacy.

Both MDR1 and NPY are soluble molecules involved in epilepsy; however, their effects on epilepsy diagnosis, treatment efficacy assessment, and prognostication in children with epilepsy have rarely been reported. Therefore, these effects were assessed in the present study by examining the differences in relevant indexes in children with epilepsy before and after treatment.

MATERIAL AND METHODS

General data

Overall, 193 children with epilepsy who were treated in the hospital from February 2017 to March 2019 were enrolled and allocated either to group A (n = 106, 59 males and 47 females) or group B (n = 87, 47 males and 40 females). The mean ages of the children in groups A and B were 6.11 ± 2.62 and 6.38 ± 2.61 years, respectively. The inclusion criteria were as follows: patients newly diagnosed with epilepsy using computed tomography (CT), magnetic resonance imaging (MRI), and electroencephalography (EEG) (Wang *et al.*, 2017); those with complete clinical data who received no chemotherapy; those treated in the hospital following diagnosis; and those cooperating with the arrangements of the medical staff. The study was approved by the Ethics Committee of our hospital. The parents or guardians were fully informed, and they signed a consent form. Exclusion criteria were as follows: patients with other immune function diseases; heart, liver, and kidney diseases; chronic diseases; organ failure; or drug allergies. The inclusion criteria were applicable to all participants.

Treatment plan

Both groups were administered OXC (0.15 g; Wuhan Pusheng Pharmaceutical Co., Ltd.; H20130015) with an initial oral dose of 8–10 mg/kg twice a day. The dose prescribed by the attending doctor was increased according to the patient's condition; however, it was maintained below 46 mg/kg. Group A was additionally administered LEV (0.5 g; Chongqing Shenghuaxi Pharmaceutical Co., Ltd.; H20143179) with an initial oral dose of 5–10 mg/kg twice a day. The dose prescribed by the attending doctor was increased according to the patient's condition; however, it was maintained below 50 mg/kg. All patients were treated for 6 months.

Experimental procedure

Fasting peripheral blood (5 mL) samples were obtained from all children the morning after admission and at 6 months after treatment. Following heparin anticoagulation, lymphocyte separation solution was used for centrifugation at 1500 r/min for 20 min. White blood cells were absorbed into the centrifuge tube, and total RNA was subsequently extracted according to the kit instructions. The concentration and purity of RNA were determined using an ultraviolet spectrophotometer (Pubiao Equipment Technology Co., Ltd., Dongguan, China, SPCC). Overall, 5 μg of total RNA was extracted and reversely transcribed with cDNA as per manufacturer instructions (HaiGene Detection Co., Ltd., Harbin, China, D0401). Polymerase chain reaction (PCR) was performed using SYBR Premix Ex Taq TM kit (Saihonggrui Biotechnology Co., Ltd., Nanjing, China, DRR041A) with a PCR system (Wuxi MicroSep Biotechnology Co. Ltd., Wuxi, China, TC9639). PCR amplification cycle was performed as follows: predegeneration at 95°C for 10 min, degeneration at 95°C for 15 s, and annealing/extension at 60°C for 60 s, for a total of 40 cycles. Three repeated cycles were employed for each sample, and the experiment was conducted for three times. The $2^{-\Delta\Delta CT}$ method was used for data analysis (Chen *et al*., 2016). U6 was used as the internal reference. Fasting venous blood (5 mL) samples that were drawn from all children the morning after admission and at 6 months after treatment were placed in EDTA-K2 anticoagulant tubes and then centrifuged at 3000 r/min for 20 min. A total of 500 μL of the upper part of the serum sample was collected and stored in an Eppendorf tube. Further, serum NPY level was determined using enzyme-linked immunosorbent assay (ELISA) according to the manufacturer instructions in the NPY kit (Nanjing Sciben Biotechnology Co., Ltd.; AT19620S/M). Standard wells, sample wells to be tested, and blank control wells (without sample and enzymatic reagent) were set up in plates. A total of 50 μL of the sample was accurately added to the standard well on the enzyme-labeled plate. In the sample well to be tested, 40 μL of sample diluent was first added, followed by 10 μL of the sample to be tested (1:5 dilution), covered with membrane, and incubated at 37ºC for 30 min. The liquid from each well was discarded, patted dry, and washed repeatedly for five times. Further, 50 μL of enzyme-labeled reagent was added to each well except the blank control ones, covered with membrane, and incubated at 37ºC for 30 min. Following this, 50 μL of chromogenic agent A and 50 μL of chromogenic agent B were respectively added to each well, mixed well, and developed in the dark at 37ºC for 10 min. Stop buffer (50 μL) was added to each well to terminate the reaction. The absorbance (OD value) of each well was sequentially measured at a wavelength of 450 nm using a BioTek automatic marker (Beijing Image Trading Co., Ltd., Beijing, China), and the NPY level was calculated. Using the origin software, the ELISA samples were set up for multi-well detection; the average absorbance of the standard and experimental group samples were obtained. The average OD value (absorbance) of the sample was subtracted from the average OD value obtained at zero concentration. For creating the standard curve, the four-parameter logistic function curve was created on the logarithmic coordinate chart that included the standard concentration on the X-axis and the corresponding OD value on the Y-axis.

Outcome measures

Treatment efficacy was assessed as follows: no seizure or complete control during treatment was considered complete remission (CR), reduction in seizure frequency by 75%–99% as partial remission (PR), reduction in seizure frequency by 50%–74% as stable disease (SD), and reduction in seizure frequency by <50% as progressive disease (PD). According to treatment efficacy observed in the two groups, CR, PR, and SD were used to determine the total effective rate, which was calculated as follows: total effective rate = (CR + PR + SD) / total cases × 100%.

Moreover, adverse reactions in both groups were recorded during epilepsy treatment.

Statistical analysis

SPSS 20.0 [EasyBio (Beijing) Technology Co., Ltd.] was used for statistical analyses. Countable data

expressed as the number of cases/percentage [n (%)] were analyzed using a chi-squared test. Measurement data were expressed as mean ± standard deviation values. Groups A and B were compared using a *t*-test; comparisons before and after treatment were performed using a paired *t*-test. A receiver operating characteristic (ROC) curve was used to assess the predictive value of serum MDR1 and NPY levels for epilepsy diagnosis, treatment efficacy assessment, and prognostication in children with epilepsy. Multivariate logistic regression analysis was used to determine the risk factors for poor prognosis in children with epilepsy. GraphPad Prism 6 was applied to construct graphs. A *P*-value of <0.05 indicated a significant difference.

RESULTS

General data

There was no significant difference between groups A and B in terms of general data—sex, age, residence, nationality, seizure type, delivery mode, disease course, premature delivery, psychomotor development, cranial MRI, and etiology (*P* >0.05; Table I).

TABLE I - Comparison of general data [n (%); x ± SD]

Classification	Group A (n = 106)	Group B (n = 87)	t/χ^2	P
Sex			0.052	0.820
Male	59 (55.66)	47 (54.02)		
Female	47 (44.34)	40 (45.98)		
Age (years)			0.714	0.476
	6.11 ± 2.62	6.38 ± 2.61		
Residence			2.587	0.108
Urban	67 (63.21)	45 (51.72)		
Rural	39 (36.79)	42 (48.28)		
Nationality			0.716	0.398
Han	54 (50.94)	39 (44.83)		
Minority	52 (49.06)	48 (55.17)		
Epilepsy type			0.875	0.349
Self-limited focal seizure	51 (48.11)	51 (58.62)		
Idiopathic generalized seizure	55 (51.89)	36 (41.38)		
Delivery mode			2.398	0.122
Vaginal delivery	63 (59.43)	42 (48.28)		
Cesarean section	43 (40.57)	45 (51.72)		
Course of disease (months)			1.285	0.200
	7.34±4.42	8.16±4.40		
Premature delivery			0.024	0.876
Yes	73 (68.87)	59 (67.82)		

TABLE I - Comparison of general data [n (%); x ± SD]

Classification	Group A (n = 106)	Group B (n = 87)	t/χ^2	P
No	33 (31.13)	28 (32.18)		
Psychomotor development			2.513	0.113
Normal	68 (64.15)	46 (52.87)		
Abnormal	38 (35.85)	41 (47.13)		
Cranial MRI			0.695	0.405
Normal	44 (41.51)	31 (35.63)		
Abnormal	62 (58.49)	56 (64.37)		
Etiology			0.122	0.998
Structural etiology	21 (19.81)	16 (18.39)		
Infectious etiology	19 (17.92)	17 (19.54)		
Genetic etiology	26 (24.53)	21 (24.14)		
Metabolic etiology	22 (20.75)	18 (20.69)		
Immune etiology	18 (16.98)	15 (17.24)		

Serum MDR1 and NPY levels

There was no significant difference in serum MDR1 and NPY levels between groups A and B before treatment ($P > 0.05$). After treatment, serum MDR1 level remarkably decreased; moreover, compared with group B, group A exhibited a significantly lower MDR1 level ($P < 0.05$). Serum NPY level remarkably increased after treatment; compared with group B, group A showed a significantly higher NPY level ($P < 0.05$; Figure 1).

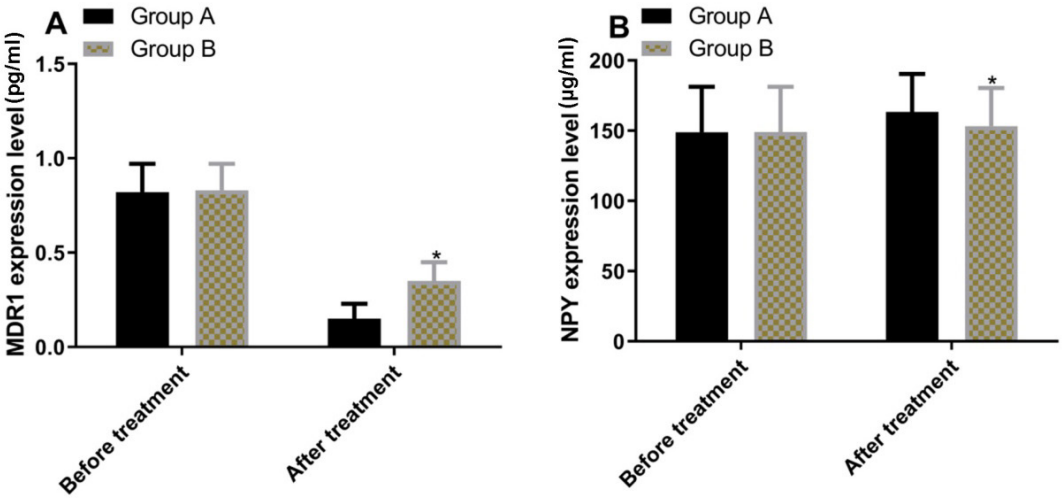

FIGURE 1- Serum MDR1 and NPY levels before and after treatment.

(A) Serum MDR1 levels before and after treatment in groups A and B. (B) Serum NPY levels before and after treatment in groups A and B. Note: compared with group B after treatment, *$P < 0.05$.

Comparison of treatment efficacy

Treatment efficacy in group A was as follows: the number of cases showing CR, PR, SD, and PD was 55 (51.89%), 29 (27.36%), 16 (15.09%), and 6 (5.66%), respectively, with the total effective rate of 94.34%. Treatment efficacy in group B was as follows: the number of cases showing CR, PR, SD, and PD was 36 (41.38%), 18 (20.69%), 20 (22.99%), and 13 (14.94%), respectively, with the total effective rate of 85.06%. Treatment was effective in both groups; however, compared with group B, treatment efficacy in group A was greater ($P = 0.031$, $\chi^2 = 4.638$).

Comparison of safety outcomes

After treatment, there were 2 cases (1.89%) of dizziness, 2 (1.89%) of somnolence, 1 (0.94%) of rash, 1 (0.94%) of emotional instability, and 1 (0.94%) of cognitive dysfunction in group A, with a total adverse reaction rate of 6.60%. Meanwhile, there were 4 cases (4.60%) of dizziness, 3 (3.45%) of somnolence, 2 (2.30%) of rash, 2 (2.30%) of emotional instability, and 4 (4.60%) of cognitive dysfunction in group B, with a total adverse reaction rate of 17.24%. Therefore, adverse reactions occurred in both groups after treatment; however, the total adverse reaction rate was significantly lower in group A than in group B ($P = 0.280$, 0.497, 0.449, 0.449, 0.112, and 0.021, $\chi^2 = 1.166$, 0.462, 0.574, 0.574, 2.529, and 5.354, respectively).

Serum MDR1 and NPY levels for predicting treatment efficacy

Children with epilepsy were divided into two groups according to different treatment efficacies: effective group (EG, n = 174) and ineffective group (IG, n = 19). After examination, it was observed that compared with patients in the IG, those in the EG exhibited significantly lower serum MDR1 levels and significantly higher serum NPY levels ($P < 0.05$). Moreover, ROC curves demonstrated that the areas under the curve (AUCs) of MDR1 and NPY for ineffective treatment prediction were 0.867 and 0.834, respectively, indicating their high predictive values (Figure 2).

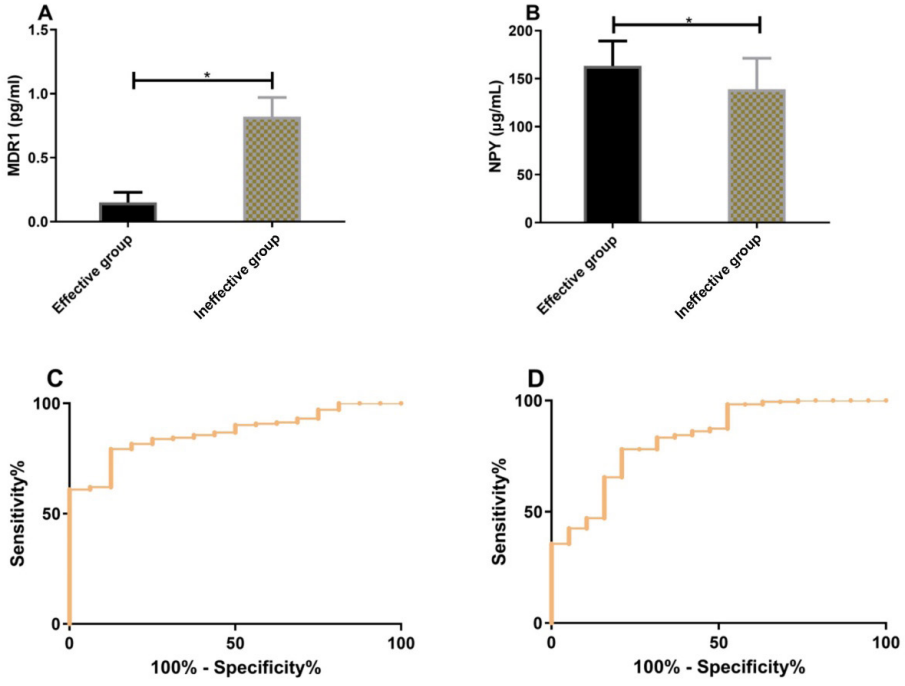

FIGURE 2- Serum MDR1 and NPY levels for predicting treatment efficacy.

(A) Serum MDR1 levels in the effective group was significantly lower than those in the ineffective group. (B) Serum NPY levels in the effective group was significantly higher than those in the ineffective group. (C) Serum MDR1 levels for predicting efficacy. (D) Serum NPY levels for predicting efficacy. Note: *$P < 0.05$.

Serum MDR1 and NPY levels for predicting poor prognosis

According to the therapeutic effect observed within 1 year, 155 children were enrolled in the stable prognosis group (SPG) and 38 in the recurrent group (RG). Compared with patients in the RG, those in the SPG exhibited significantly lower serum MDR1 levels and significantly higher serum NPY levels ($P < 0.05$). ROC curves showed that the AUCs of MDR1 and NPY for predicting recurrence were 0.916 and 0.829, respectively, indicating their high predictive values (Figure 3).

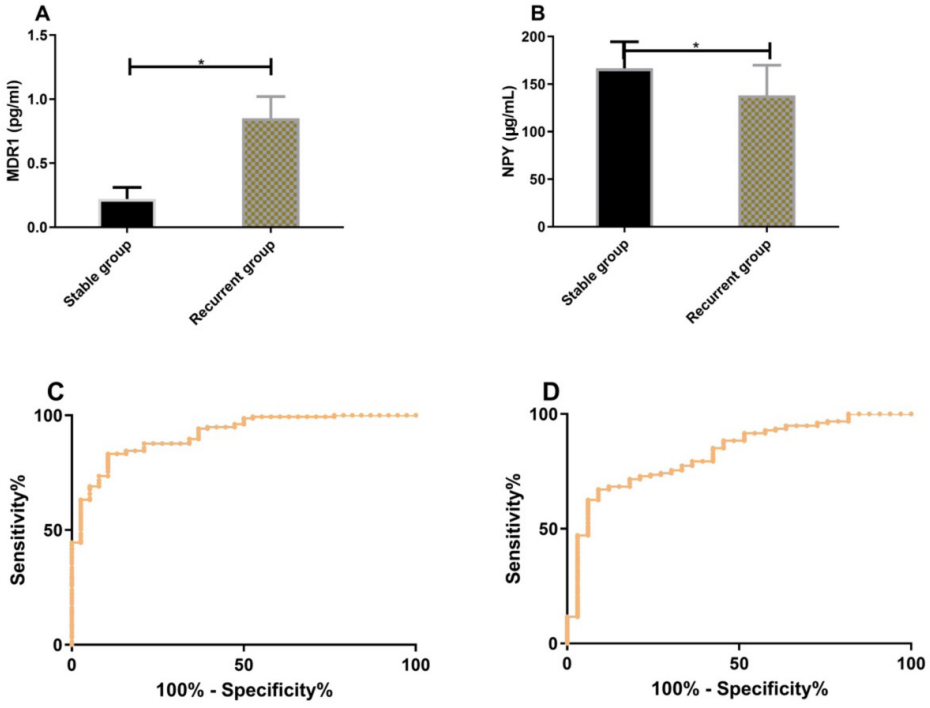

FIGURE 3 - Predictive value of serum MDR1 and NPY levels for poor prognosis in children with epilepsy.

(A) Serum MDR1 levels in the stable prognosis group was significantly lower than those in the recurrent group. (B) Serum NPY levels in the stable prognosis group was significantly higher than those in the recurrent group. (C) Serum MDR1 levels for predicting treatment efficacy. (D) Serum NPY levels for predicting treatment efficacy. Note: *$P < 0.05$.

Univariate analysis of poor prognosis in children with epilepsy

Univariate analysis revealed no significant differences in terms of sex, age, psychomotor development, and cranial MRI between the SPG and RG ($P > 0.05$); however, significant differences were observed in terms of seizure type, etiology, EEG abnormalities, intracranial hemorrhage, neonatal convulsion, premature delivery, and serum MDR1 and NPY levels ($P < 0.05$; Table II).

TABLE II - Univariate analysis of poor prognosis in children with epilepsy [n (%); x ± SD]

Classification	Stable prognosis group (n = 155)	Recurrent group (n = 38)	t/χ^2	P
Sex			1.983	0.159
Male	89	17		
Female	66	21		
Age (years)			0.146	0.884
	6.21 ± 2.65	6.28 ± 2.64		
Epilepsy type			13.371	0.001
Self-limited focal seizure	92 (59.35)	10 (26.32)		
Idiopathic generalized seizure	63 (40.65)	28 (73.68)		
Psychomotor development			0.283	0.595
Normal	93 (60.00)	21 (55.26)		
Abnormal	62 (40.00)	17 (44.74)		
Cranial MRI			0.688	0.407
Normal	58 (37.42)	17 (44.74)		
Abnormal	97 (62.58)	21 (55.26)		
Etiology			19.184	0.001
Structural etiology	22 (20.75)	15 (17.24)		
Infectious etiology	26 (24.53)	10 (11.49)		
Genetic etiology	43 (40.57)	4 (4.60)		
Metabolic etiology	37 (34.91)	3 (3.45)		
Immune etiology	27 (25.47)	6 (6.90)		
EEG abnormality			6.004	0.014
Yes	56 (36.13)	22 (57.89)		
No	99 (63.87)	16 (42.11)		
Intracranial hemorrhage			28.661	<0.001
Yes	42 (27.10)	28 (73.68)		
No	113 (72.90)	10 (26.32)		
Neonatal convulsion			10.151	0.001
Yes	78 (50.32)	30 (78.95)		
No	77 (49.68)	8 (21.05)		
Premature delivery			7.759	0.005
Yes	67 (43.23)	26 (68.42)		
No	88 (56.77)	12 (31.58)		

TABLE II - Univariate analysis of poor prognosis in children with epilepsy [n (%); x ± SD]

Classification	Stable prognosis group (n = 155)	Recurrent group (n = 38)	t/χ^2	P
MDR1 (pg/mL)			44.890	<0.001
	0.14 ± 0.05	0.88 ± 0.18		
NPY (μg/mL)			6.217	<0.001
	143.28 ± 28.08	168.89 ± 21.28		

Multivariate analysis of poor prognosis in children with epilepsy

Seizure type, etiology, EEG abnormalities, intracranial hemorrhage, neonatal convulsion, premature delivery, and serum MDR1 and NPY levels were used as independent variables, and poor prognosis was used as the dependent variable in a multivariate analysis; a logistic regression model was used for this analysis. The results showed that EEG abnormalities, intracranial hemorrhage, neonatal convulsion, premature delivery, and serum MDR1 and NPY levels were independent risk factors for poor prognosis in children with epilepsy (Table III).

TABLE III - Multivariate logistic regression analysis of poor prognosis in children with epilepsy

Factor	β	S.E.	Wald	P	OR	95% CI	Variable	Assignment
Epilepsy type	0.123	0.032	3.674	0.069	0.482	0.155–1.274	X1	No = 0, yes = 1
Etiology	0.621	0.252	6.835	0.087	1.133	0.362–4.251	X2	No = 0, yes = 1
EEG abnormality	0.338	0.108	9.935	0.032	1.399	1.137–1.736	X3	No = 0, yes = 1
Intracranial hemorrhage	0.338	0.108	9.935	0.032	3.484	2.427–4.819	X4	No = 0, yes = 1
Neonatal convulsion	1.161	0.507	4.768	0.019	3.46	2.223–7.612	X5	No = 0, yes = 1
Premature delivery	1.239	0.557	5.023	0.020	4.591	3.729–5.537	X6	No = 0, yes = 1
MDR1 (pg/mL)	1.345	0.478	5.308	0.004	6.213	2.314–12.827	X7	Data were continuous variables and raw data were used for analysis.
NPY (μg/mL)	0.756	0.298	6.584	0.012	2.217	1.231–3.816	X8	Data were continuous variables and raw data were used for analysis.

DISCUSSION

Epilepsy is one of the most disabling neurological disorders. Although several AED regimens have been employed in the clinical setting, approximately 30% of patients with epilepsy continue to experience seizures (Schmidt *et al.*, 2016). Zhibin *et al.* found that although LEV and OXC monotherapy achieved good therapeutic effects in children with epilepsy, their combined use significantly reduced epileptic seizures, as determined

based on EEG findings, and had a higher safety (Zhibin, Jiang, Xiao, 2016); these findings are consistent with the findings of the present study. The total effective rate in group A was higher than that in group B. The results indicated that LEV plus OXC combination exerted a significant therapeutic effect on pediatric epilepsy; moreover, the incidence of adverse reactions after treatment in group A was significantly lower than that in group B, indicating that this combination was an effective and safe treatment for epilepsy in children.

In a study by Chen *et al.* (Chen *et al.*, 2015), high NPY levels were observed in the cerebrospinal fluid and plasma of patients with refractory epilepsy, and these levels were effectively reduced following treatment with LEV. This finding is similar to the results of the present study in that the upregulated serum MDR1 levels in children with epilepsy significantly decreased after treatment in both groups, with group A showing a significantly greater decrease compared with group B. In addition, the downregulated serum NPY levels in children with epilepsy significantly increased after treatment in both groups, with group A showing a significantly higher increase compared with group B. The findings of the present study demonstrated that serum MDR1 and NPY level may prove to be beneficial for the early diagnosis of epilepsy in children. Treatment efficacy prediction showed that compared with patients in the IG, those in the EG exhibited significantly lower serum MDR1 levels and significantly higher NPY levels before treatment. The AUCs of MDR1 and NPY for ineffective treatment prediction were 0.867 and 0.834, respectively, suggesting a high predictive value of serum MDR1 and NPY levels for treatment efficacy assessment in children with epilepsy. The subsequent analysis of prognosis showed that compared with patients in the RG, those in the SPG exhibited significantly lower serum MDR1 levels and significantly higher serum NPY levels after treatment. The AUCs of MDR1 and NPY for recurrence prediction were 0.916 and 0.829, respectively, indicating the high predictive value of serum MDR1 and NPY levels for poor prognosis in children with epilepsy. Finally, univariate and multivariate analyses were performed on factors influencing poor prognosis; the results showed that EEG abnormalities, intracranial hemorrhage, neonatal convulsion, premature delivery, and serum MDR1 and NPY levels were independent risk factors for poor prognosis in children with epilepsy.

This study confirmed that serum MDR1 and NPY levels exhibited high predictive values for early disease diagnosis, treatment efficacy assessment, and prognostication in children with epilepsy treated with LEV plus OXC combination. However, there is still some limitations. For example, a larger patient population and comparison with healthy controls should be included to improve the accuracy and universality of the findings of the present study. In addition, claims data provide information on whether a prescription was filled but not whether the child took the medication and adhered to the guidelines. Furthermore, correlations between serum MDR1 and NPY levels and treatment options were not examined at the cellular level; therefore, cell biology experiments should be conducted in the future.

In conclusion, serum MDR1 and NPY levels have high predictive values for early disease diagnosis, treatment efficacy assessment, and prognostication in children with epilepsy treated with LEV plus OXC combination; this could be used to develop more effective monitoring tools to predict the outcomes of different treatment options.

\CONFLICTS OF INTEREST

The author declares no conflict of interest.

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None.

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