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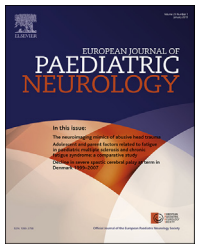

Original article

Usefulness of perampanel with concomitant levetiracetam for patients with drug-resistant epilepsy

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ABSTRACT

Purpose: The purpose was to evaluate the efficacy of treatment and the occurrence of aggression-related adverse events among children receiving perampanel (PER) with concomitant levetiracetam (LEV).

Methods: Patients were selected according to the following criteria: 1) between 12 and 18 years old; 2) seizures refractory to at least 2 first-line drugs; 3) at least 4 seizures a month before PER administration; and 4) at least 12 months of follow-up. Patients were subdivided into groups with and without LEV as concomitant treatment. PER was administered at a dose of 2 mg/day, increasing by 2 mg/day every 2 weeks up to 12 mg/day if seizures appeared. In comparison with the baseline seizure frequency, response to PER treatment was classified as follows: complete cessation (100% seizure control); response (≥50% reduction in seizures); and exacerbation (≥50% increase in seizures). Responders were identified as patients showing complete cessation or response.

Results: The study group comprised 39 outpatients with a mean age of 13.7 years at enrollment. Responder status was seen in 13 of the 19 patients with LEV and 4 of the 20 patients without LEV. PER appeared significantly more effective in patients with LEV than in those without LEV ($p = 0.0076$). Seizure-free status was significantly more frequent among patients with LEV (47.4%) than among those without LEV (15.0% ($p = 0.0407$)). Aggression was present in 2 patients without LEV, but none with LEV.

Conclusion: The present study suggests the utility of PER with concomitant LEV for children with drug-resistant epilepsy.

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1. Introduction

Drug-resistant epilepsy represents a significant burden for patients, associated with reduced quality of life (QOL).[1] Anti-epileptic drug (AED)-resistant epilepsy is evident in 20–30% of patients with seizure disorders. These uncontrolled epilepsies carry significant risks for individual patients. In addition, patients with uncontrolled seizures also incur far greater healthcare costs than patients whose seizures are in remission.[2] On the other hand, participants in many studies have been institutionalized children with epilepsy with frequent seizures and/or epilepsy syndromes associated with structural brain lesions.[3] The prefrontal lobe appears more highly vulnerable to repeated seizures than other cortical regions, which can lead to cognitive and behavioral disturbances in children with epilepsy.[4] Accordingly, treatment to achieve seizure remission as soon as possible may be required to achieve the optimal prognosis for children with cognitive/behavioral problems.[5]

Various new AEDs have been introduced in many countries, including Japan. Despite the continued development of AEDs, the number of refractory epilepsy cases has not fallen dramatically since the early 1990s.[6] In fact, AED-resistant epilepsy is still evident in 20–30% of patients with seizure disorders. The objective of pharmacotherapy for epilepsy is freedom from seizures without bothersome adverse events (AEs). There is a clear need for the development of AED medications with novel mechanisms of action that have the potential to improve outcomes even in severe and refractory cases.[7]

Perampanel (PER) is an orally administered, highly selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor antagonist.[8] Randomized control trials have shown a favorable efficacy and safety profile compared with placebo,[9] and once-daily PER (4–12 mg/day) has been approved in Japan as an adjunctive therapy for partial-onset seizures in patients > 12 years old. In double-blind, placebo-controlled Phase III clinical trials, treatment with PER was well tolerated and, as in focal seizure studies, resulted in a significantly greater reduction in seizure frequency compared to placebo.[10]

On the other hand, levetiracetam (LEV) is one of the new AEDs with a novel mechanism of action on the synaptic vesicle protein SV2A.[11] Published studies on the use of LEV in children and adolescents with epilepsy aged between 4 and 14 years have shown an excellent pharmacokinetic and tolerability profile, with few deleterious effects on cognitive function and no known pharmacokinetic interactions.[12] However, emotional and behavioral AEs have often been reported by users of LEV, occurring in 7–40% of children and adolescents aged between 4 and 16 years.[13] In another study by Mohanraj et al., 5% of patients developed behavioral problems requiring withdrawal of LEV.[14] Accordingly, attention must be paid to these AEs in children and adolescent cases with LEV administration.

Although previous studies have suggested that treatment with PER may be well tolerated overall, the United States Prescribing Information (USPI) for PER includes a boxed warning for serious psychiatric and behavioral reactions.[15,16] In addition, patients treated with PER have experienced greater rates of hostility- and aggression-related AEs that were severe and led to dose reduction, interruption, and discontinuation more frequently than placebo-treated patients.[15] These AEs have also been observed with LEV. The Warnings and Precautions section of the USPI noted that LEV-treated patients are at risk for irritability and aggression.[17] It is important to note that AEs such as aggression and irritability are not exclusive to PER. However, the efficacy and AEs for adolescents treated with PER with concomitant LEV have not been investigated fully. Accordingly, the purpose of the present study was to evaluate the efficacy and occurrence of irritability and aggression-related AEs among adolescents receiving PER therapy with concomitant LEV.

2. Materials and methods

Patients were recruited from among epilepsy outpatients of the authors' hospital and selected according to the following criteria: 1) between 12 years and 18 years old; 2) seizures refractory to at least 2 first-line AEDs; 3) at least 4 seizures a month during the 3 months before PER administration; and 4) at least 12 months of follow-up. Personal and family histories were registered, and neurological examinations were performed on all patients. Seizures were classified in accordance with the International League Against Epilepsy classification of epileptic seizures and epileptic syndromes.[18,19] Electroencephalograms (EEGs) were recorded during spontaneous sleep, arousal, and wakefulness when possible. All patients underwent brain magnetic resonance imaging. Biochemical analyses and screening for metabolic disorders were performed in all patients. Chromosomal investigations were carried out when considered necessary.

Patients were subdivided into the following two groups in accordance with the presence of LEV as concomitant treatment: either with LEV (LEV(+)) or without LEV (LEV(−)). Data from patients in these two groups admitted to our hospital between June 01, 2016 and December 31, 2017 were retrospectively reviewed. All individuals were evaluated longitudinally, clinically, and by EEG. Exclusion criteria were: 1) poor compliance by parents/caregivers in completing diary records of seizure frequency, AEs and completion of scheduled visits; or 2) problems setting the baseline period and a need to take other approaches in addition to treatment with AED because of progressive neurological and/or severe medical disorders. In addition, patients with evidence of persistent non-adherence to pharmacotherapy and those with concurrent neurologic or other chronic disorders were also excluded. Careful clinical and EEG follow-up for at least 12 months was performed in all cases, and all children were re-evaluated at the end of follow-up.

PER was administered at a once-daily dose of 2 mg/day for the first 2 weeks, followed by a dose of 4 mg/day for the second 2 weeks. The dose of PER was increased by 2 mg/day every 2 weeks if seizures appeared. In the absence of seizure appearance, the dose of PER was not changed. During this period, PER doses could be increased to 12 mg/day, in accordance with the judgment of the clinician. All patients treated with PER underwent follow-up visits at regular intervals every

2 weeks. Concomitant treatment was not modified during PER administration.

The 3 months before starting treatment was established as the baseline period. Seizure frequency, type, and duration, as well as AEs, were recorded in an epilepsy diary completed by the parents and/or caregivers. Seizure frequency was defined as the mean seizure frequency per month. Twelve months after the end of the dose increment period for maintenance, response was assessed. In comparison with the baseline seizure frequency and severity, response to PER treatment was classified as follows: complete cessation, 100% seizure control; response, ≥50% reduction in seizures; minimal response, >25% to <50% reduction in seizures; no response, <25% reduction in seizures to <50% increase in seizures; and exacerbation, ≥50% increase in seizure frequency. Seizure-free status was interpreted as complete cessation of seizures for more than 3 months. Responders were identified as patients showing complete cessation or response. Tolerability and AEs were assessed by documenting AEs spontaneously reported by the parents, caregivers, and/or child. AEs were classified as major or minor in accordance with severity. Major AEs were defined as events leading to cessation of PER. AEs that proved tolerable with modification of the dosing scheme, symptomatic or supportive management, or behavioral modification were considered as minor AEs. Adherence was assessed by direct questioning and physical examination. The entire treatment period was lasted more than 12 months after PER administration.

Statistical analyses were performed using SPSS version 19 software (IBM, New York, NY). Continuous variables are presented as mean ± standard deviation (SD). Student's t-test, the chi-square test or Fisher's exact test was used, as appropriate, for analysis of between-group differences in discrete variables. Logrank test was used for analysis of Kaplan–Meier curve. Values of $p < 0.05$ were defined as statistically significant.

This study was performed in accordance with the Declaration of Helsinki. Approval from our local ethics committee was obtained for this research. All participants and their parents were provided with full details about the protocol and informed consent was obtained prior to enrollment.

3. Results

The study group comprised 41 outpatients at enrollment. Of these, 2 patients (1 male, 1 female) who were lost to follow-up were excluded. Data from the remaining 39 children with epilepsy aged between 12 and 18 years (mean, 13.6 years) were analyzed. Demographic characteristics of all participants are presented in Table 1. All the consecutive patients were included. All patients treated with AEDs other than LEV and PER showed drug concentrations within the reference range.

Demographic characteristics of subjects in each treatment group are presented in Table 2. The LEV(+) group comprised 19 children with epilepsy aged between 12 and 18 years. In contrast, the LEV(−) group comprised 20 children with epilepsy aged between 13 and 18 years. Age, sex distribution, age at epilepsy onset, duration of epilepsy, and presence of mental retardation showed no significant differences within groups

Table 1 – Clinical characteristics of participants in the present study.

Characteristics	Participants
Patients enrolled, *n* (%)	39
Gender	
Male, *n* (%)	21 (53.8)
Female, *n* (%)	18 (46.2)
Age at onset, yr; mean (range)	5.20 (0.3–9)
Duration of epilepsy, yr, mean (range)	8.61 (5.3–12.3)
Presence of mental retardation	15 (mild, 8; moderate, 2; severe, 5)
Prior psychiatric history	5
Epileptic syndrome, *n* (%)	
ILRE	4 (10.3)
CLRE	9 (23.1)
SLRE	21 (53.8)
Unclassified	3 (7.7)
Undetermined (CSWS)	2 (5.1)
Number of prior AEDs, mean (range)	4.9 (2–7)
Number of concomitant AEDs, mean (range)	2.46 (2–3)

ILRE, idiopathic localization-related epilepsy; CLRE, cryptogenic localization-related epilepsy; SLRE, symptomatic localization-related epilepsy; CSWS, epilepsy with continuous spikes and waves during slow sleep; AED, anti-epileptic drug.

($p = 0.58$, $p > 0.09$, 0.82, 0.96, and 0.09, respectively). Five patients (3 patients in the LEV(+) and 2 patients in the LEV(−) group) had a history of psychiatric illness such as autism spectrum disorder. No significant difference in presence of prior psychiatric history was evident between treatment groups ($p = 0.66$).

When classified according to electroclinical syndromes, no significant difference in epilepsy syndrome was evident between treatment groups ($p = 0.27$). Focal to bilateral tonic-clonic seizures were present in 14 patients (73.7%) in the LEV(+) group and 15 patients (75.0%) in the LEV(−) group. In addition, no significant difference in number of prior or concomitant AEDs was evident between treatment groups ($p = 0.43$ and 0.44, respectively). All patients treated with carbamazepine, valproate sodium and zonisamide displayed drug concentrations within the appropriate reference ranges (mean trough concentrations of 7.9, 72.8, and 20.2 μg/mL, respectively). In contrast, mean dosages and concentrations of LEV in LEV(+) patients were 2164.7 mg/day and 22.4 μg/mL, respectively.

As shown in Table 3, seventeen patients (43.6%) were considered as overall responders. In 6 patients, the drug had been tapered off because of inefficacy or the appearance of AEs such as drowsiness. In the remaining 16 patients, the drug had been continued because of minimal response. The effective dosage of PER in the 17 responders demonstrated a wide range (mean, 6.94 mg/day; range, 4–12 mg/day).

Moreover, efficacy of PER varied according to the presence or absence of concomitant LEV. With concomitant LEV, 13 of 19 patients (68.4%) were considered responders, compared to only 4 of 20 patients (20.0%) without LEV (Table 4). PER

Table 2 – Demographic characteristics of subjects in each treatment group.

Characteristics	LEV(–)	LEV(+)	*p*-Value
Patients enrolled, *n* (%)	20	19	
Mean age (years)	13.4	13.7	0.580
Gender			
Male, *n* (%)	11 (55.0)	10 (52.6)	>0.99
Female, *n* (%)	9 (45.0)	9 (47.4)	
Age at onset, mean (range)	5.1 years (5 months-9 years)	5.3 years (4 months-9 years)	0.825
Mean duration of epilepsy (years)	8	8.2	0.962
Presence of mental retardation	7 (severe 2, moderate 1, mild 4)	8 (severe 3, moderate 1, mild 4)	0.094
Epileptic syndrome, *n* (%)			
Idiopathic focal	2 (10.0)	2 (10.5)	
Cryptogenic	5 (25.0)	4 (21.1)	
Symptomatic focal	10 (50.0)	11 (57.9)	0.274
Unclassified	3 (15.0)	0 (0.0)	
Undetermined	0 (0.0)	2 (10.5)	
Mean number of prior AEDs	4.4	4.6	0.430
Mean number of concomitant AEDs	2.6	2.7	0.442

LEV, levetiracetam; MR, mental retardation; sev, severe; mo, moderate; mi, mild; SLRE, symptomatic localization-related epilepsy; CLRE, cryptogenic localization-related epilepsy; AED, anti-epileptic drug.

Table 3 – Clinical efficacy and adverse effects of PER.

Patients enrolled, *n* (%)	39
Efficacy	
Seizure-free	12 (30.8)
Responder	5 (12.8)
Minimal response	16 (41.0)
No-response	6 (15.4)
Exacerbation	0 (0.0)
Total responders	17 (43.6)
Adverse events	
Present	5 (12.8)
Drowsiness	3 (7.7)
Aggression	2 (5.1)
Requirements for withdrawal	0 (0.0)

PER, perampanel.

Table 4 – Clinical efficacy and adverse effects of PER.

	LEV(–) ($n = 20$)	LEV(+) ($n = 19$)	*p*-Value
Efficacy			
Seizure response			
Complete cessation	3 (15.0%)	9 (47.4%)	0.0407
Response	1 (5.0%)	4 (21.1%)	
Total responder	4 (20.0%)	13 (68.4%)	0.0076
EEG response			
Response	3 (15.0%)	13 (68.4%)	0.0011
Adverse events			
Presence	3 (15.0%)	2 (10.5%)	>0.999
Aggression	2 (5.1%)	0 (0.0%)	
Absence	17 (85.0%)	17 (89.5%)	

PER, perampanel; LEV, levetiracetam.

appeared significantly more effective in patients with LEV than in those without LEV ($p = 0.0076$). In addition, the rate of seizure-free patients was significantly higher in patients with LEV (47.4%) than in those without LEV (15.0%; $p = 0.0407$) (Table 4).

Seizure reduction was demonstrated over a relatively wide range of epilepsy syndromes. PER appeared effective against both focal epilepsy (14/34, 41.2% of participants; 14/17, 82.4% of responders) and unclassified/undetermined epilepsy (3/5, 60.0% of participants; 3/17, 17.6% of responders). Three of the 4 patients with idiopathic (non-lesional) focal epilepsy were responsive to treatment, as were 11 of 14 patients with symptomatic/cryptogenic focal epilepsy. Both responders among patients with undetermined epilepsy had epilepsy with continuous spikes and waves during slow sleep (CSWS).

The effect of PER on the frequency of interictal epileptiform discharges was revealed in at least some patients. In 16 of 39 patients (41.0%), a consistent and major decrease was seen in the frequency of interictal epileptiform discharges. Regarding the efficacy for EEG paroxysmal abnormality, PER appeared significantly more effective in patients with LEV (13/19, 68.4% of participants) than in those without LEV (3/20, 15.0% of participants; $p = 0.0011$) (Table 4).

Mean interval to achievement of seizure/EEG response after PER administration in the LEV(–) and LEV(+) groups were 7.8/9.0 and 5.9/6.9 months, respectively. Efficacy for seizure and EEG was achieved more rapidly in the LEV(+) group than in the LEV(–) group ($p = 0.0006$, 0.0003, respectively) (Fig. 1).

Mean doses of PER in LEV(+) and LEV(–) groups were 7.7 and 9.1 mg/day, respectively. Mean effective doses of PER in LEV(+) and LEV(–) groups were 6.5 and 8.5 mg/day, respectively. The effective dose of PER tended to be lower in patients with LEV than in those without LEV, although this difference was not significant ($p = 0.074$).

AEs occurred in 5 patients (12.8% of the total treatment group). Treatment-related AEs were drowsiness and aggression. Drowsiness was mild in 3 patients, all of whom showed a rapid decrease in drowsiness when PER dosage was reduced. The occurrence of AEs did not differ significantly between LEV(+) patients and those without LEV ($p > 0.99$). Aggression was present in 2 patients without LEV, but 0 patients with LEV. This AE in these two patients was considered minor. Results of hematological and biochemical tests were normal in all patients. None of the events causing hospitalization (aggravated

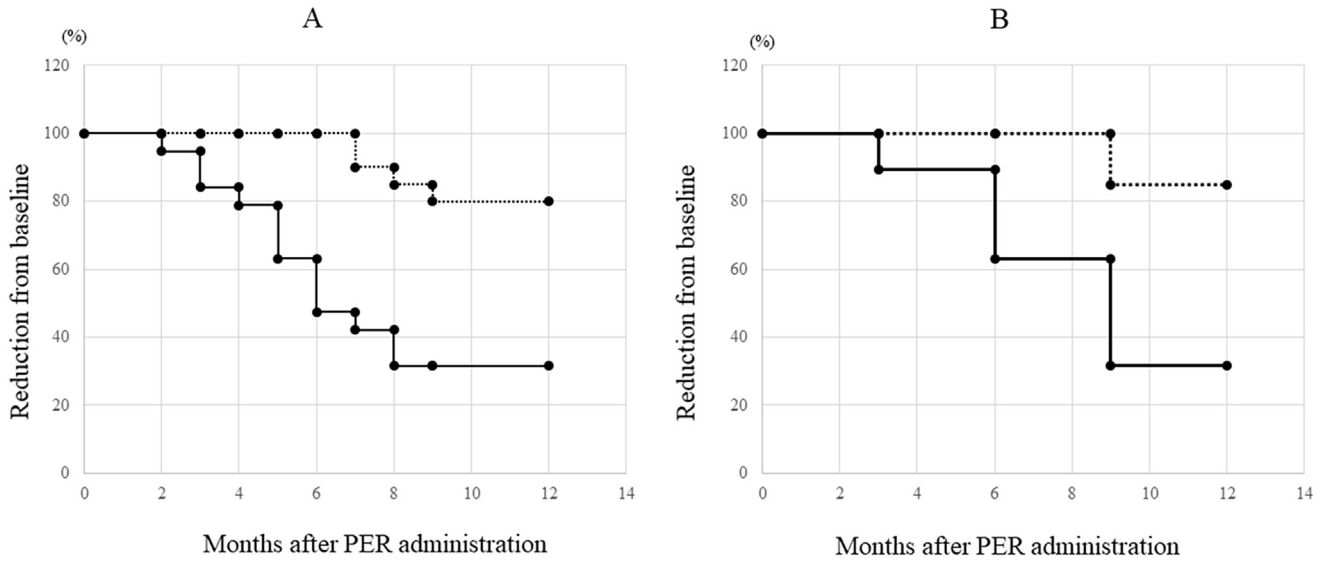

Fig. 1 – Kaplan–Meier curves for probability of seizure (A) and EEG paroxysmal abnormality (B) reduction after administration of PER. Efficacy for seizure and EEG was achieved more rapidly in the LEV(+) group than in the LEV(−) group ($p = 0.0006$, 0.0003, respectively). Sequential plots for LEV(−) (dotted lines) and LEV(+) (solid lines). EEG, electroencephalogram; PER, perampanel; LEV, levetiracetam.

convulsions; lower respiratory infections; otitis media; sinusitis; and vomiting) was considered by the investigators as related to the study medication.

Cognitive measurements were performed before the PER administration period and 12 months later in 18 patients. None revealed significantly decreased full intelligence quotient (IQ), verbal IQ, or performance IQ.

No clinically relevant drug-related changes were seen in clinical laboratory values, including LEV blood level, vital signs, physical examination, neurological assessment, or electrocardiography during the study.

4. Discussion

The aim of the present study was to determine whether concomitant use of PER and LEV in children with focal epilepsy was associated with enhancement of treatment efficacy and increased risk of AEs such as irritability and aggression. The present study was based on clinical practice and provided new insights into the use, efficacy, and AEs of PER in children with refractory epilepsy. This study showed that PER appeared more effective against focal epilepsy in cases with concomitant LEV. Furthermore, the present study also showed that the rates of AEs such as irritability and/or aggression did not increase in cases of concomitant PER and LEV.

A previous study based in Germany showed a lower frequency of freedom from seizures at 6 months (15%) compared to the present study (30.8%).[18] In contrast, responder rate at 6 months was higher in that study (50%) than in the present study (43.6%). In another study by Coyle et al.,[19] no patients achieved freedom from seizures. However, that study showed a responder rate of 28%, similar to that in a study by Steinhoff et al.[18] In the present study, secondary generalized seizures were reduced by 72.7% after 12 months of PER, similar to the ≤62.9% reduction in this seizure type in randomized controlled trials[20] and the 76.5% reduction in a study of primary generalized seizures in idiopathic generalized epilepsy.[10] The variety of refractory patients or those with prior AEDs in the present study seem likely to explain this discrepancy in efficacy outcomes.

Reductions in seizure frequency and responder rates were greater in patients receiving concomitant LEV than in those not receiving concomitant LEV. This may be because the effect of PER is strengthened in the presence of LEV. In vitro studies have shown that PER is a selective AMPA receptor, thus using a novel pharmacological mechanism. On the other hand, the newly discovered mechanism of action for LEV is unique among AEDs, and has led to the development of new compounds with binding at the SV2A site.[21] In a previous study, PER consistently provided greater reductions in seizure frequency among patients receiving the four commonly co-administered AEDs (CBZ, valproate sodium, lamotrigine, and LEV).[20] However, efficacy was lower when the inducer CBZ was co-administered compared with any of the other three non-inducer AEDs. In addition, that study also showed that the 50% responder rate for all partial seizures was higher when LEV was co-administered compared with any of the other three AEDs,[20] agreeing with the findings of the present study. This may be because LEV is not an inducer AED, lacks interactions with other AEDs, and some other pharmacokinetic interaction with LEV and PER is present. Further longitudinal studies are needed to confirm these issues.

In this study, 4 patients with idiopathic focal epilepsy were included, which could introduce a strong bias because of a self-limited epilepsy precisely in this age range. However, these 4 patients were not typical, but atypical evolution of benign focal epilepsy of childhood. Moreover, the results were still significant

if these patients excluded ($p = 0.0059$ as total responder and $p = 0.0016$ as EEG responder). Accordingly, the inclusion of these patients was considered not to introduce a bias.

The most frequently reported AEs emerging from treatment with PER were dizziness, somnolence, fatigue, irritability, nausea, and falls, which were mild in severity in the majority of patients.[22] Among these AEs, irritability and aggression were more frequently reported in the psychiatric domain by patients on PER compared with those taking placebo. Moreover, these reactions have been observed in patients both with and without concomitant use of medications associated with hostility and aggression.[15,23] Several reports have indicated that LEV may cause neuropsychiatric manifestations such as aggressiveness. Thus, the risk of AEs such as irritability and aggression is likely to be increased in cases of concomitant PER and LEV. However, the results in this study showed that concomitant use of PER with LEV did not increase the risk of behavioral abnormalities and psychotic symptoms. The selectivity of PER for AMPA receptors over NMDA receptor antagonists may be an important feature clinically, since NMDA receptor antagonists are known to produce psychoactive effects, including schizophrenia-like symptoms and cognitive impairment.[24] In a previous study by Chung et al., although hostility- and aggression-related AEs were numerically greater during concomitant use of PER with LEV compared to non-concomitant use of PER with LEV, the difference was not significant.[25] They also showed that similar or slightly lower rates of severe AEs were observed in PER patients receiving LEV compared to patients not receiving LEV.[25] These findings suggest that concomitant treatment with LEV has no appreciable effect on the occurrence of hostility- or aggression-related AEs in patients receiving PER, in agreement with our results.

On the other hand, the occurrence of AEs related to aggression and hostility may be observed in patients both with and without a history of psychiatric/aggressive behavior.[15] In the present study, 5 patients had a history of aggressive behavior. One patient who presented with aggression after PER administration had a history of aggressive behavior. However, another patient who presented with aggression after PER administration had no prior history. The present study suggests that the occurrence of AEs related to aggression was observed in patients with and without prior history of aggressive behavior, in agreement with the study by Chung et al.[25] Moreover, another 4 patients with a history of aggressive behavior had reduction of aggression after PER administration. LEV may have positive effects on cognition and behavior in patients with frontal lobe epilepsy.[26] Similarly, PER may have positive effects on the behavior by reducing seizures in at least some patients with epilepsy. Further longitudinal studies are needed to confirm these issues.

One limitation of this study was that a potential confounding factor is variation in concomitant LEV dose. The average dose of concomitant LEV across PER dose groups was generally consistent based on approximations of the doses reported by patients. However, no detailed analyses were performed. In addition, this study was also limited by the relatively small number of patients in the treatment groups analyzed. Patients could also have received concomitant AEDs other than LEV, which may not have been accounted for in this analysis. Our findings thus need to be replicated with larger study samples.

5. Conclusions

The present results suggest the usefulness of PER in concomitant treatment with LEV for seizure reduction in children with drug-resistant epilepsy. PER is well tolerated as an adjunctive therapy, including concomitant use with LEV. However, as this was not a controlled study, firm conclusions cannot be drawn. Prospective controlled studies on larger sample sizes are needed.

Ethical approval

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest

Dr. Hideaki Kanemura has received speaker's fees from Eisai Co., Ltd and Otsuka Pharmaceutical Co., Ltd. None of the other authors have any conflicts of interest to disclose.

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