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Efficacy and Safety of Lamotrigine Adjunctive Therapy in Lennox-Gastaut Syndrome

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Purpose: Lamotrigine (LTG) is often used as adjunctive therapy in Lennox-Gastaut syndrome (LGS); however, it may worsen myoclonic and atypical absence seizures in LGS patients. This study reviewed the overall efficacy and safety of LTG in children with LGS.

Methods: This retrospective study included 38 patients (aged <18 years) with LGS who underwent LTG adjunctive therapy between October 2020 and March 2022 at Severance Children's Hospital. The primary outcome was the change in seizure frequency at 3, 6, and 12 months after starting LTG treatment. A favorable treatment response was defined as a ≥50% reduction in seizure frequency.

Results: The main seizure semiology at the start of treatment was tonic-clonic in 15 (39.5%) patients, spasm in 14 (36.8%), atonic in five (13.2%), myoclonic in three (7.9%), and absence in one (2.6%). The median number of anti-seizure medications (ASMs) was 3.95 (interquartile range, 3 to 4.75). The most common concomitant ASMs were valproate (35/38, 92.1%), levetiracetam (23/38, 60.5%), and topiramate (20/38, 52.6%). After 3 months, seizure frequency was reduced by >50% in 47.4% of patients (18/38). After 6 months, 20 patients (20/36, 55.6%) showed a favorable response. After 12 months, five patients (5/11, 45.5%) responded to treatment. Three patients showed myoclonic seizures at the start of treatment and >50% amelioration in seizure frequency at the 3- and 6-month follow-up visits.

Conclusion: This study reaffirms the efficacy and safety of LTG in children with LGS. Therefore, LTG is strongly recommended as an adjunctive therapy for children with LGS.

Keywords: Lennox Gastaut syndrome; Lamotrigine; Anticonvulsants

Introduction

Lennox-Gastaut syndrome (LGS) is a severe type of developmental epileptic encephalopathy characterized by (1) multiple types of drug-resistant seizures with onset at age <18 years (one of which must include tonic seizures); (2) cognitive and often behavioral impairments (which may be absent at seizure onset); and (3) diffuse slow spike-and-wave and generalized paroxysmal fast activity on electroencephalography (EEG) [1-3]. Gastaut et al. [1] first described LGS in 1966, and advances in treating this intractable type of epilepsy remain challenging, as there are no fundamental guidelines on how to treat LGS. In most cases, multimodal treatment is required, including polytherapy with anti-seizure medications (ASMs), cannabidiol, surgical intervention, and/or a ketogenic

diet [4].

The U.S. Food and Drug Administration has approved five drugs to treat LGS since 1993: clobazam, felbamate, lamotrigine (LTG), rufinamide, and topiramate. A recent Cochrane review summarized that adjunctive therapy with LTG and rufinamide resulted in a significant reduction in seizure frequency in patients with LGS [5]. LTG has proven to be a broad-spectrum ASM with significant efficacy in reducing tonic, tonic-clonic, and atonic seizures [6-12]. However, there are conflicting reports on the therapeutic effect of LTG in myoclonic and atypical absence seizures [6-8]. This study makes a novel contribution to the literature by providing additional evidence regarding the overall efficacy and safety of LTG as an adjunctive therapy for LGS in children.

Materials and Methods

1. Patient selection

This single-center retrospective study was conducted on 38 children who were diagnosed with LGS and received LTG as an adjunctive therapy between October 2020 and March 2022 at Severance Children's Hospital, Seoul, South Korea.

The patient inclusion criteria were as follows: (1) age at last follow-up <18 years; (2) diagnosis of LGS according to the 2022 International League Against Epilepsy (ILAE) classification and definition of epilepsy syndromes [3]; (3) minimum duration of follow-up ≥3 months after initiation of LTG; and (4) no previous history of LTG administration. Patients were excluded if they were diagnosed with focal epilepsy and had significant abnormalities in liver or kidney function.

2. Clinical characteristics of patients

Patient demographics such as age, sex, and race were analyzed. The seizure semiology and etiology of epilepsy were investigated according to the 2017 ILAE operational classification of seizure types and epilepsies [13,14]. EEG was analyzed for the cerebral background and epileptiform discharges [15]. The EEG background activity was defined as: (1) normal; (2) mild (fewer posterior alpha rhythms in an awake state with or without minor irregularities or excessively slow waves); (3) significant (abnormalities of up to 50% during one continuous EEG session); and (4) marked (abnormalities of >50%). EEG epileptiform discharges were classified according to the frequency of epileptiform discharges: (1) none/rare; (2) occasional; (3) frequent (up to 50% of epileptiform discharges during one continuous EEG session); and (4) marked (>50% in one session).

3. Route of LTG administration and dosage specifications

LTG was administered orally in the form of tablets, chewable tablets, or orally disintegrating tablets. The LTG dosage was weight-based. Initially, children whose body weight was <30 kg received 0.5 to 1 mg/kg/day in two divided doses, while those with a body weight ≥30 kg received 25 to 50 mg/day in two divided doses. When titrating the drug, the LTG dosage was increased by 0.5 to 2.0 mg/kg/day at 1 to 2 weeks intervals in children with a body weight <30 kg. Those with a body weight ≥30 kg were given LTG doses increasing by 2.0 mg/kg/day at 1 to 2 weeks intervals. During the maintenance period, children with a body weight of <30 kg were administered LTG at 5 to 10 mg/kg/day. Precautions were taken in children receiving concomitant valproate (VPA). Patients receiving VPA were administered LTG at a dose of 1 to 5 mg/kg/day. Patients with a body weight of ≥30 kg received a maintenance dose of 100 to 200 mg LTG/day.

4. Treatment outcome

The primary treatment outcome was the change in seizure frequency at 3, 6, and 12 months after LTG initiation. A favorable treatment response to medication was defined as follows: (1) responder: seizure-free or ≥50% reduction in seizure frequency; (2) non-responder: <50% reduction in seizure frequency, no change, or seizure aggravation. Patients were not considered to have made progress if additional therapeutic interventions, such as a trial of a new ASM or cannabidiol, or surgery was performed after LTG administration. Patient progress was investigated using medical records and seizure diaries, and missing data were collected through phone calls.

5. Safety and tolerability

The safety and tolerability of LTG were evaluated based on the incidence of adverse events, changes in clinical laboratory parameters, vital signs, neurological examinations, and additional visits to the emergency room or hospitalization.

6. Statistical analysis

SPSS version 26.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Descriptive statistics were reported, including the median, standard deviation, and interquartile range (IQR). The proportion of patients was reported as a percentage. The chi-square and independent t-tests were performed to identify clinically significant characteristics associated with treatment outcomes. The Fisher exact test and Pearson correlation coefficients were used for further analyses. The requirement for informed consent was waived by the Institutional Review Board (IRB). The study was conducted in accordance with the ethical standards of the IRB

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of Severance Children's Hospital (4-2022-1261) and the Helsinki Declaration of 1964, as revised in 2000.

Results

1. Clinical characteristics of patients

A total of 38 patients were included in this study. The median age at seizure onset was 2.56 years (IQR, 0.50 to 4.0). The most common etiologies of LGS were structural (17/38, 44.7%) and unknown (14/38, 36.8%). Structural causes included congenital brain malformations (9/17, 52.9%), hypoxic-ischemic encephalopathy (6/17, 35.3%), and traumatic brain injuries (2/17, 11.8%). Seizure semiology at diagnosis revealed spasms in 18 patients (47.4%) and tonic-clonic seizures in 13 (34.2%). The most common seizure semiology at the start of LTG treatment was tonic-clonic seizures (15/38, 39.5%) and spasms (14/38, 36.8%). In addition, atonic seizures occurred in five patients (13.2%), myoclonic seizures in three (7.9%), and absence seizures in one (2.6%). The concurrent seizure semiology consisted of myoclonic seizures in five patients (13.2%) and tonic-clonic or absence seizures in two (5.3%). The EEG background was mild in three patients (7.9%) and significant in 35 patients (92.1%). The EEG epileptiform discharges were marked in five patients (13.2%), frequent in 24 patients (63.2%), occasional in eight patients (21.1%) and rare in one patient (2.6%). However, EEG abnormalities were not statistically proven to be related to treatment outcomes (Table 1).

The median number of ASMs was 3.95 (IQR, 3 to 4.75). The most common concomitant ASMs were VPA (35/38, 92.1%), levetiracetam (23/38, 60.5%), and topiramate (20/38, 52.6%). Eighteen (47.4%), 14 (36.8%), and 21 (55.3%) patients had a history of ketogenic diet, cannabidiol use, and epilepsy surgery, respectively (Table 2).

2. Treatment outcomes

At the 3-month follow-up, a >50% reduction in seizure frequency was achieved in 47.4% of patients (18/38). At the 6-month follow-up, 20 (20/36, 55.6 %) patients showed a favorable response. At the 12-month follow-up, five patients (5/11, 45.5%) responded to the treatment. Three patients showed myoclonic seizures at the start of treatment and >50% amelioration in seizure frequency at the 3- and 6-month follow-up visits. One patient with absence seizures at the start of treatment also showed favorable seizure outcomes during the same period (Table 3). Four of the five patients who manifested concurrent myoclonic seizures presented with favorable seizure outcomes at the 6-month follow-up. Two patients with concurrent absence seizures also showed good outcomes at the 6- and 12-month follow-up visits (Supplementary Table 1).

Table 1. Patient characteristics at initiation of lamotrigine adjunctive therapy

Variable	Total (n = 38)	*P* value
Male sex	24 (63.2)	0.36
Age at seizure onset (yr)	2.56 ± 3.01 (0.5–4.0)	0.31
Etiology		1.00
Structural	17 (44.7)	
Genetic	5 (13.2)	
Immune	2 (5.3)	
Unknown	14 (36.8)	
Main seizure semiology at treatment		0.06
Atonic	5 (13.2)	
Myoclonic	3 (7.9)	
Tonic-clonic	15 (39.5)	
Spasm	14 (36.8)	
Absence	1 (2.6)	
Concurrent seizure semiology		1.00
Atonic	1 (2.6)	
Myoclonic	5 (13.2)	
Tonic-clonic	2 (5.3)	
Spasm	1 (2.6)	
Absence	2 (5.3)	
Baseline EEG BG		1.00
Mild	3 (7.9)	
Significant	35 (92.1)	
Baseline EEG ED		0.15
Rare	1 (2.6)	
Occasional	8 (21.1)	
Frequent	24 (63.2)	
Marked	5 (13.2)	

Values are presented as number (%) or mean±standard deviation (range).
EEG, electroencephalography; BG, background; ED, epileptiform discharge.

Table 2. Treatment history at initiation of lamotrigine adjunctive therapy

Variable	Total (n = 38)	*P* value
Age at start of lamotrigine (yr)	8.24 ± 5.19 (4–11.75)	0.07
Number of ASMs	3.95 ± 1.25 (3–4.75)	0.39
Concomitant ASMs		
VPA	35 (92.1)	0.23
LEV	23 (60.5)	0.46
TPM	20 (52.6)	0.76
RUF	18 (47.4)	0.33
PB	15 (39.5)	0.46
CLB	7 (18.4)	0.41
VGB	7 (18.4)	1.00
History of a ketogenic diet	18 (47.4)	0.32
History of steroids	22 (57.9)	0.02
History of cannabidiol	14 (36.8)	0.08
History of surgery		0.89
VNS	3 (7.9)	
CC	15 (39.5)	
Resective surgery	4 (10.5)	

Values are presented as mean±standard deviation (range) or number (%).
ASM, anti-seizure medication; VPA, valproate; LEV, levetiracetam; TPM, topiramate; RUF, rufinamide; PB, phenobarbital; CLB, clobazam; VGB, vigabatrin; VNS, vagal nerve stimulation; CC, corpus callostomy.

Table 3. Treatment outcomes according to the main seizure semiology

	After 3 months	After 6 months	After 12 months
Responders	18/38 (47.4)	20/36 (55.6)	5/11 (45.5)
Atonic (% total atonic)	4/5 (80.0)	4/5 (80.0)	1/2 (50.0)
Myoclonic	3/3 (100.0)	3/3 (100.0)	
Tonic-clonic	5/15 (33.3)	6/14 (42.8)	2/5 (33.3)
Spasm	5/14 (35.7)	6/13 (46.1)	2/4 (50.0)
Absence	1/1 (100.0)	1/1 (100)	

Values are presented as number (%).

3. Safety and tolerability

No significant adverse events were observed following LTG administration. Three patients experienced adverse events, including pruritus (1/3, 33.3%), hirsutism (1/3, 33.3%), and irritability (1/3, 33.3%). None of the patients experienced severe skin rashes or neurological symptoms, such as diplopia or ataxia.

Discussion

LTG, 6-(2,3-dichlorophenyl)- 1,2,4-triazine-3,5-diamine, is a phenyltriazine, whose exact mechanism of action has not been fully elucidated. The most probable mechanism is that LTG selectively inhibits voltage-gated sodium channels that stabilize presynaptic neuronal membranes by inhibiting the presynaptic release of excitatory amino acids, such as glutamate and aspartate, which has been proven *in vitro* and *in vivo* [16-18].

Many previous studies have reported the efficacy of LTG in adults and children [9]. However, this study is significant as there are limited patient cohorts after the early 2000s that provide up-to-date evidence regarding the effectiveness of LTG in pediatric patients with LGS. A double-blind placebo clinical trial by Motte et al. [6] demonstrated in 1997 that 33% of LTG-treated patients with LGS showed seizure reductions, compared with 16% in the placebo group. Farrell et al. [8] pointed out that LTG reduced seizure frequency by >50% in 54% (30/56) of patients with generalized epilepsy and 73% (11/15) of children with LGS. Other studies have also provided evidence that upon LTG initiation, more than half of the patients with LGS showed a >50% reduction in total seizure frequency [7,10,11,19]. Consistent with previous reports, our study also demonstrated that approximately half of the children with LGS showed a favorable response to adjunctive therapy with LTG at 6 and 12 months.

LTG effectively reduces tonic, tonic-clonic, clonic, atonic, and typical absence seizures [6-8,10,11,19,20]. However, the therapeutic effect of LTG in myoclonic and atypical absence seizures is a matter of debate. It is noteworthy that our patients did not experience the aggravation of either absence or myoclonic seizures after LTG administration, which was consistent with previous studies [7,20]. However, Motte et al. [6] reported that LTG did not significantly reduce atypical absence seizures. Some studies have also shown evidence of aggravation of myoclonic seizures with LTG administration [7,8,21]. In patients with generalized epilepsy, high serum LTG levels were associated with a prolonged aggravation of myoclonic seizures [22-24]. However, the mechanism behind this is unclear. It appears that cortical and negative myoclonus are aggravated by LTG [25-28]. However, LTG showed favorable outcomes in myoclonus associated with typical 3-Hz spike-and-wave discharges, such as myoclonic astatic epilepsy, juvenile myoclonic epilepsy, and myoclonic absence [12,29,30]. Further studies are needed to evaluate the pathophysiology of this association.

For newly diagnosed LGS patients, the 2022 National Institute for Health and Care Excellence guidelines proposed LTG as second-line monotherapy or add-on treatment after a VPA trial [31]. A recent Cochrane review and expert panels have confirmed the effectiveness of VPA and adjunctive therapy with LTG in children with LGS [2,5,32-35]. VPA inhibits LTG metabolism, more specifically hepatic glucuronidation, whereas carbamazepine and phenytoin induce this process [18,36]. In the present study, 92.1% of LGS patients received VPA concomitantly, and 54.5% of these patients had a significant (>50%) reduction in seizure frequency. It is noteworthy that our study showed that LTG was effective, not only in newly diagnosed LGS, but also in severe forms of LGS already treated with multiple ASMs, especially in patients on VPA.

A recent network meta-analysis of ASM in patients with LGS suggested that more efficacious ASM therapy was associated with a higher possibility of adverse events and eventual drug discontinuation. LTG showed the highest probability of adverse events [37]. Nonetheless, our study did not show any significant adverse events associated with LTG administration. Previous studies have reported rash, pharyngitis, fever, drowsiness, ataxia, and cardiac arrhythmia [6,8,10,38,39]. Farrell et al. [8] reported that rashes occurred more frequently in patients treated with concomitant VPA [19]. However, our study showed fewer, less severe adverse events than previous studies.

This study had several limitations. First, this was a retrospective observational study; further prospective, randomized, controlled studies are needed to confirm these findings. Second, this was a single-center study, and the number of patients was too small to obtain statistically significant outcomes. Finally, follow-up studies of EEG and neuropsychiatric tests for cognitive/behavioral development would have added more value to the study.

However, there are few effective ASMs for LGS, a medically refractory epilepsy syndrome that adversely affects the developmen-

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tal, mental health, and socioeconomic status of patients. Therefore, it is important to reaffirm the efficacy of existing ASMs for the treatment of these patients. In conclusion, our study highlighted the efficacy and safety of LTG in children with LGS. This study adds to the current knowledge regarding ASM treatment in patients with LGS, whose seizures are mostly intractable.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.26815/acn.2022.00437.

Conflicts of interest

Hoon-Chul Kang is an associate editor, Ara Ko, Se Hee Kim, Joon Soo Lee, and Heung Dong Kim are editorial board members of the journal, but They was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Conceptualization: HCK. Data curation: HJS and HCK. Formal analysis: HJS and AK. Funding acquisition: HJS and HCK. Methodology: HJS and AK. Project administration: HJS and HCK. Visualization: HJS and AK. Writing-original draft: HJS. Writing-review & editing: HJS, AK, SHK, JSL, HDK, and HCK.

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