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Treatment strategies for Lennox-Gastaut syndrome: outcomes of multimodal treatment approaches

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Abstract

Background: Multimodal treatment approaches are often considered for patients with Lennox-Gastaut syndrome (LGS). Creating an algorithm that can guide healthcare providers in selecting treatment options for patients with LGS remains a challenge. Herein, we assessed the long-term seizure-free and neurodevelopmental outcomes of stepwise multimodal treatment in patients with LGS.

Objective: Herein, we assess the long-term seizure-free and neurodevelopmental outcomes of stepwise multimodal treatment in patients with LGS.

Methods: We retrospectively examined the data of 371 patients with LGS who underwent stepwise multimodal treatment, including antiseizure medication (ASM) therapy, dietary therapy (DT), resective epilepsy surgery (R-ES), and palliative epilepsy surgery (P-ES). The seizure-free outcome was considered to be the effect of the final treatment according to the treatment algorithm, and the percentage of patients who remained seizure-free in each treatment group was calculated. ASM treatment, DT, R-ES, and P-ES were applied to 371 (100%), 201 (54.2%), 112 (30.2%), and 115 (31.0%) patients with LGS, respectively. We evaluated the stepwise multimodal treatment outcomes in these patients.

Results: One hundred sixty-eight patients (45.3%) remained seizure-free for at least 1 year (seizure-free-for-1-year group), 61 of whom (16.5%) remained seizure-free for more than 5 years (remained-seizure-free group). Among the patients treated with ASM therapy, DT, R-ES, and P-ES, 41 (11.1%), 53 (14.3%), 56 (15.1%), and 29 (7.8%), respectively, remained seizure-free for 1 year. In addition, 15 (4.1%), 15 (4.1%), 19 (5.1%), and 12 (3.2%) patients in the ASM, DT, R-ES, and P-ES treatment groups, respectively, remained seizure-free for more than 5 years. Both the seizure-free-for-1-year and remained-seizure-free groups showed significant improvement in electroencephalography findings and neurodevelopmental status following treatment.

Conclusion: This study provides an update on the long-term seizure outcomes and neurodevelopmental improvements in a large cohort of patients with LGS following comprehensive multimodal treatment. We emphasize that the active combination of multiple ASMs, DT, and surgical treatment could provide long-term seizure-free outcomes and significant neurological benefits to patients with LGS.

Keywords: epilepsy, epilepsy surgery, Lennox-Gastaut syndrome, multimodal treatment

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Introduction

Lennox-Gastaut syndrome (LGS) is a typical developmental epileptic encephalopathy that is mainly diagnosed during childhood. It is a devastating disorder that causes medically intractable seizures and progressive intellectual disability (ID) with severe electroencephalogram (EEG) abnormalities.[1–3] The clinical progression of LGS can vary greatly depending on a wide range of underlying causes, including genetic, structural, and metabolic causes.[4,5]

LGS treatment remains challenging because the symptoms in a large proportion of patients with LGS are not controlled, even with the multimodal approach. In addition to the combined application of numerous antiseizure medications (ASMs), dietary therapy (DT) such as ketogenic diet (KD) and various surgical approaches have been attempted in patients with LGS. Although these multidisciplinary treatments exhibit limited effectiveness, a standard treatment protocol for LGS has not yet been established, and LGS remains one of the most challenging epileptic encephalopathies to treat.[6–12] Several previous studies have described the combination of treatment modalities for LGS; however, these studies were limited by small sample size and inconsistent treatment algorithms.[13–15] Therefore, it is important to establish an effective treatment plan for patients with LGS.

This study aimed to analyze treatment flow in a large cohort of patients with LGS and evaluate the outcomes based on the provision of multidisciplinary treatment according to a certain treatment algorithm in a clinical setting. The treatment strategies for LGS and their outcomes evaluated in this study could serve as a reliable reference for treating patients with LGS in the future.

Methods

Patients

We retrospectively reviewed the medical charts of patients with LGS who underwent treatment at Severance Children's Hospital, Republic of Korea, between 2004 and 2019. The diagnostic criteria for LGS were as follows: (1) presence of multiple types of seizures, including generalized tonic seizures combined with myoclonic, drop attack, atonic, atypical absence, and focal seizures; (2) severe EEG abnormalities including generalized paroxysmal fast activities (GPFAs) and/or diffuse slow spike-wave complexes during wakefulness or asleep status; and (3) progressive cognitive impairment.[1–3] Patients who were diagnosed with LGS before the age of 18 years and followed up for at least 1 year after treatment initiation were included in the study. Patients were excluded if they had the following: (1) progressive degenerative neurological disorders other than epileptic encephalopathy; (2) proven metabolic disorders, including mitochondrial cytopathies; (3) other well-defined syndromes (such as tuberous sclerosis complex); and (4) electroclinical syndromes other than LGS (such as Dravet syndrome with a confirmed *SCN1A* mutation).[8,16]

Evaluation of patients with LGS

Data on EEG and magnetic resonance imaging (MRI) findings, seizure type, etiology, number of ASMs ever used, therapeutic modalities, and seizure-free duration after the final treatment were retrospectively evaluated for all patients. We classified the LGS etiology based on the results of brain MRI, laboratory studies, and genetic tests, such as diagnostic exome sequencing. The long-term seizure-free outcome was defined as remaining seizure-free for more than 5 years. After treatment initiation, patients were divided into two groups based on the seizure-free duration. Patients who remained seizure-free for more than 1 year were included in the 'seizure-free-for-1-year' group, and those who remained seizure-free for more than 5 years were included in the 'remained-seizure-free' group. In addition, patients who experienced a seizure after remaining seizure-free for 1 year were included in the 'seizure-relapse' group, and those who were never seizure-free were included in the 'seizure-persist' group.[17] In addition, among the patients who could not achieve seizure-free with ASMs alone, patients who refused diet therapy and epilepsy surgery for various reasons were classified as 'never seizure-free group'.

We assessed seizure outcomes based on caregivers' reports and seizure diaries at each visit. Additional demographic and clinical data were obtained from medical charts. Based on the underlying etiology, patients with LGS were divided into 'structural', 'genetic', and 'unknown' groups, according to the revised terminology and concepts of the International League Against Epilepsy.[18] The structural-etiology group included two categories: (1) acquired destructive brain damage and (2) malformations of cortical development (MCD). The unknown-etiology group included patients who showed normal results on MRI, genetic testing, and metabolic laboratory evaluation.

Treatment algorithm for patients with LGS

The treatment principle for LGS was based on a stepwise multimodal approach. The treatment algorithm used in this study is shown in Figure 1.

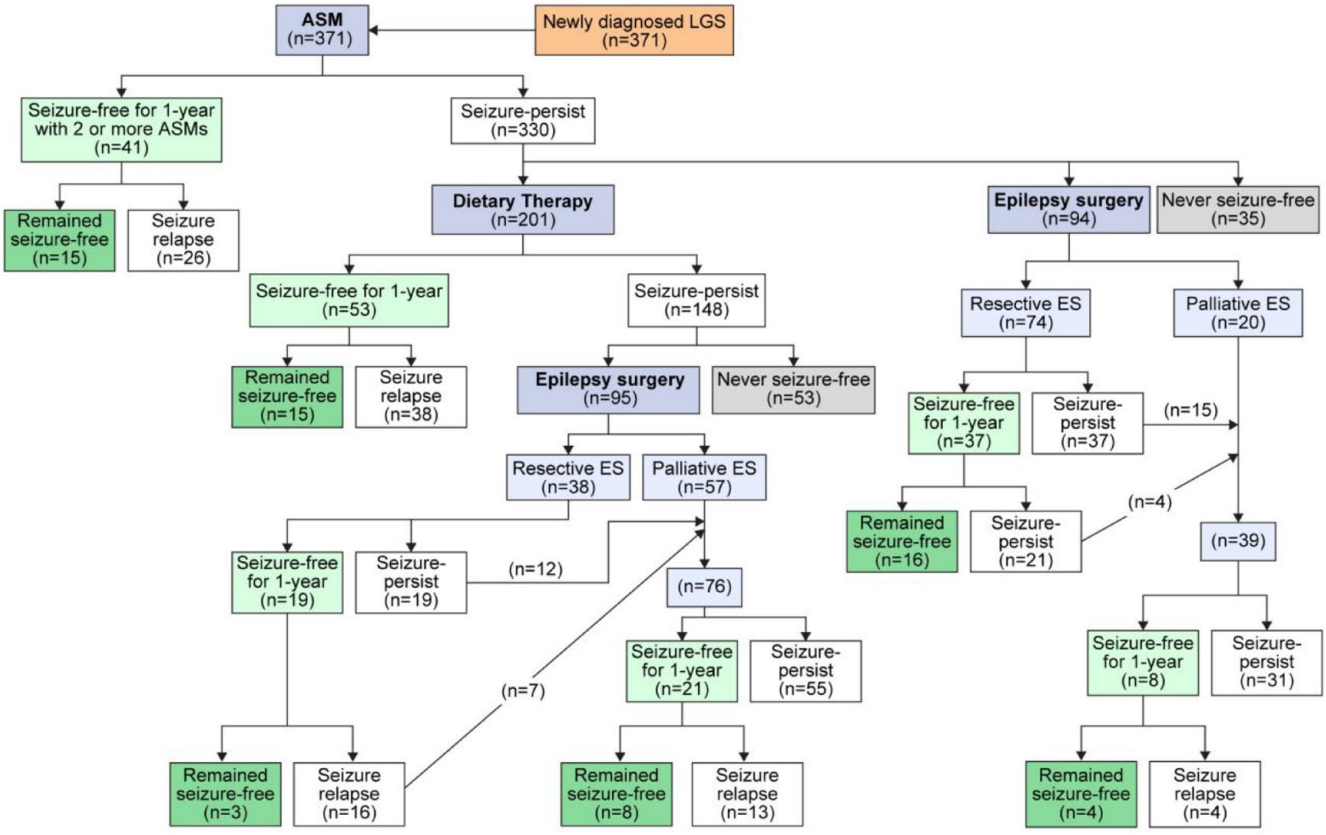

Figure 1. Algorithm for multimodal treatment in 371 patients with LGS.
ASMs, antiseizure medications; ES, epilepsy surgery; LGS, Lennox-Gastaut syndrome.

In this algorithm, the direction of the arrows indicates the treatment flow, and the branch points without an arrow indicate that no additional follow-up treatment was performed.[18]

All patients with LGS were initially treated with at least two ASMs. For patients who did not remain seizure-free for 1 year with the use of more than two ASMs, DT or epilepsy surgery was considered based on the results of additional examinations. DT was based on a classical KD with a lipid:non-lipid ratio of 4:1 or 3:1, and KD variants, such as the modified Atkins diet (MAD) and low glycemic index (LGI) diet, were applied according to the patients' tolerance. Of the 201 patients who received DT, 169 were treated with the classical KD; 27, MAD; and 5, LGI diet. Epilepsy surgery was additionally considered for patients who did not remain seizure-free for 1 year even after receiving DT.[19]

Epilepsy surgery was divided into resective epilepsy surgery (R-ES) and palliative epilepsy surgery (P-ES). R-ES was classified as unilobar resection, multilobar resection, or hemispherectomy, based on the findings of a pre-surgical evaluation. P-ES was performed when focal resection was not possible and included corpus callosotomy (CC) and vagus nerve stimulation (VNS). In addition, after R-ES, some patients in the seizure-relapse and seizure-persist groups underwent P-ES. This epilepsy surgery protocol was performed in the same way as the epilepsy surgery protocol performed in the seizure-persist group after applying DT.

Evaluation of treatment outcomes

We evaluated the seizure-free outcomes along with EEG findings and the neuropsychological status during the follow-up period. Through the changes in the EEG and developmental status of all LGS patients before and after treatment, we tried to confirm the trend of the overall treatment effect by applying an active stepwise multimodal approach.

In the seizure-free-for-1-year group, each patient was examined for seizure-free status, and the

EEG findings 1 year after the last treatment were evaluated according to the treatment algorithm. In the remained-seizure-free group, the seizure-free status and EEG findings at 5 years following the last treatment were evaluated.

The EEG findings were graded as follows: 1, normalization; 2, slow and disorganized background rhythm without focal or unilateral sharp wave discharges; 3, slow and disorganized background rhythm with focal or unilateral sharp wave discharges; and 4, slow and disorganized background rhythm with generalized slow spike and wave (GSSW) discharges, GPFAs, and multifocal sharp wave discharges. The EEG findings before and after the treatment were evaluated. In addition, in the seizure-persist group, the EEG findings 1 year after the final treatment, according to the treatment algorithm, were evaluated.[8,16]

We attempted to evaluate the neuropsychological status before and after treatment to the maximum possible extent. Neuropsychological assessment was performed using standard tools, such as the Bayley Scales of Infant Development and age-appropriate Wechsler scales, depending on the patient's age and intellectual capacity. We measured the developmental quotient (DQ; developmental age/chronological age) according to the Bayley Scales of Infant Development and intelligence quotient (IQ) according to the Korean-Wechsler scales for children or adolescents. The DQ and IQ were ranked as follows: normal/borderline, DQ or IQ $\geqslant$70; mild/moderate ID, DQ or IQ = 35–69; and severe/profound ID, DQ or IQ $<$35. The neuropsychological status was evaluated before treatment initiation and 1 year and 5 years after each treatment. The neuropsychological status after treatment was compared with that before treatment in the seizure-free-for-1-year and remained-seizure-free groups. In addition, in the seizure-persist group, the neuropsychological status 1 year after the last treatment according to the treatment algorithm was compared with the neuropsychological status before treatment.[16] The bar graph represents the number of patients in each group.

Data availability

Anonymized data analyzed in this study can be made available to qualified investigators upon request to the corresponding author. Our data will be available beginning 9 months and ending 36 months following article publication with investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose for individual participant data meta-analysis. Proposals may be submitted up to 36 months following article publication. After 36 months, the data will be available at our university's data warehouse but without investigator support other than deposited metadata. Information regarding submitting proposals and accessing data may be found at the link to be provided.

Statistical analyses

Continuous variables were presented as median and range (minimum–maximum), and ratios for each group were expressed as percentages. The chi-square test or Fisher's exact test was used for categorical variables, as appropriate. The statistical significance level was set at $p < 0.05$. All statistical analyses were performed using the R Statistical Software (version 4.0.5; R Foundation for Statistical Computing, Vienna, Austria).

Results

General characteristics of patients

Three hundred seventy-one patients with LGS were enrolled and retrospectively analyzed in this study. The general characteristics of the enrolled patients are shown in Table 1. The male:female ratio of patients with LGS was 61.2:38.8. The median year of follow-up duration was 13.8 years, and the median age at seizure onset was 1.2 years. The number of patients who developed seizures before 2 years of age was 224 (60.4%), and 107 (28.8%) patients had a history of infantile spasms. All patients had generalized tonic seizures; other accompanying seizure types included myoclonic (39.6%), drop attack (31.8%), atonic (14.0%), atypical absence (6.5%), and focal seizures (18.9%).

One hundred ninety-seven patients (53.1%) had a structural etiology. Among patients with structural brain abnormalities, 93 (25.1%) had destructive brain lesions, including the sequelae of central nervous system infections, periventricular leukomalacia, hypoxic–ischemic encephalopathy, and intracranial hemorrhage or infarction. Ninety-nine patients (26.7%) had MCD, such as lissencephaly, heterotopias, schizencephaly, polymicrogyria, and

focal cortical dysplasia. Diagnostic exome sequencing was performed in 45 patients, leading to the identification of genetic causes in 16 patients (4.3%). Among patients with MCD, 27 (7.3%) were diagnosed with focal cortical dysplasia based on the findings of the pathological examination, and five patients (1.4%) were diagnosed with gliosis alone. Genetic mutations affecting *CDKL5* ($n=3$), *SLC9A6* ($n=2$), *SZT2* ($n=2$), *STXBP1* ($n=1$), *KCNQ2* ($n=1$), *SCN2A* ($n=1$), *IQSEC2* ($n=1$), *KANSL1* ($n=1$), *KCNA1* ($n=1$), *SNAP25* ($n=1$), *ZEB2* ($n=1$), and *MECP2* ($n=1$) were found. However, the etiology remained unknown in 158 (42.6%) patients. The median number of ASMs ever used was 5 and ranged from 2 to 11.

Table 1. General characteristics of patients with LGS.

	Total ($n=371$)
Sex, *n* (%)	
Male	227 (61.2)
Female	144 (38.8)
Age at last follow-up (years), median (range)	13.8 (1.3–40.1)
Follow-up duration (years), median (range)	12.1 (1.1–35.2)
Age at seizure onset (years), median (range)	1.2 (0–12.0)
Early onset seizure (before 2 years of age), *n* (%)	224 (60.4)
History of infantile spasms, *n* (%)	107 (28.8)
Seizure type, *n* (%)	
Generalized tonic (tonic-clonic, clonic)	371 (100)
Myoclonic	147 (39.6)
Drop attack	118 (31.8)
Atonic	52 (14.0)
Atypical absence	24 (6.5)
Focal	70 (18.9)
Etiology, *n* (%)	
Structural	197 (53.1)
Destructive	93 (25.1)
MCD	99 (26.7)
FCD	27 (7.3)
Non-FCD	72 (19.4)
Gliosis alone	5 (1.3)
Genetic	16 (4.3)
Unknown	158 (42.6)
Number of ASMs ever used, median (range)	5.0 (2.0–11.0)

Data are presented as median (range) for continuous variables and number (%) for categorical variables. ASMs, antiseizure medications; FCD, focal cortical dysplasia; LGS, Lennox-Gastaut syndrome; MCD, malformation of cortical development.

Seizure-free outcomes of stepwise multimodal treatment and clinical factors according to the treatment method

Patients with LGS were divided into four groups according to the treatment method (the ASM, DT, R-ES, and P-ES groups), and seizure-free outcomes were evaluated (Figure 1). The seizure-free outcome was considered as the effect of the final treatment according to the treatment algorithm, and the percentage of patients in each treatment group was calculated. The ASM, DT, R-ES, and P-ES groups included 371 (100%), 201 (54.2%), 112 (30.2%), and 115 (31.0%) patients, respectively (Table 2). One hundred sixty-eight patients (45.3%) remained seizure-free for 1 year, of whom 61 (16.5%) remained seizure-free for more than 5 years. Moreover, 41/371 patients (11.1%) who received ASM treatment, 53/201 patients (26.5%) who received DT, 56/112 patients (50.0%) who underwent R-ES, and 29/115 patients (25.2%) who underwent P-ES remained seizure-free for 1 year. In addition, 15/371 patients (4.1%) who received ASM treatment, 15/201 patients (7.5%) who received DT, 19/112 patients (17.0%) who underwent R-ES, and 12/115 patients (10.4%) who underwent P-ES remained seizure-free for more than 5 years. In 15 patients who remained-seizure-free with only ASM treatment, valproic acid, lamotrigine, clobazam, and topiramate were most effective. The R-ES and P-ES groups were further divided into subgroups based on the treatment method. The most common R-ES was multilobar resection ($n=32$, 53.3% of the multilobar R-ES group) in the seizure-free-for-1 -year group and hemispherectomy ($n=6$, 24.0% of the hemispherectomy group) in the remained-seizure-free group. Regarding P-ES, CC and VNS were performed in 100 and 35 patients, respectively, and 20 patients underwent both CC and VNS. Following CC, 24.0% and 11.0% of the patients remained seizure-free for 1 year and 5 years, respectively. Fifteen patients underwent VNS

Table 2. Seizure-free outcomes with each treatment method.

	Treatment methods						
	ASMs (*n* = 371)	Dietary therapy (*n* = 201)	R-ES (*n* = 112)			P-ES (*n* = 115)	
			Unilobar (*n* = 27)	Multilobar (*n* = 60)	Hemispherectomy (*n* = 25)	CC (*n* = 100)	VNS (*n* = 35)
Seizure-free for 1 year, *n* (%)	41 (11.1)	53 (26.4)	11 (40.7)	32 (53.3)	13 (52.0)	24 (24.0)	5 (14.3)
Remained-seizure-free, *n* (%) (seizure-free for >5 years)	15 (4.1)	15 (7.5)	3 (11.1)	10 (16.7)	6 (24.0)	11 (11.0)	1 (2.9)
Seizure relapse after 1 year, *n* (%)	26 (7.0)	38 (18.9)	8 (29.6)	22 (36.7)	7 (28.0)	13 (13.0)	4 (11.4)
Persisting seizures, *n* (%)	330 (88.9)	148 (73.6)	16 (59.3)	28 (46.7)	12 (48.0)	76 (76.0)	30 (85.7)

ASMs, antiseizure medications; CC, corpus callosotomy; multilobar, multilobar resection; P-ES, palliative epilepsy surgery; R-ES, resective epilepsy surgery; unilobar, unilobar resection; VNS, vagus nerve stimulation.
'Remained-seizure-free' was defined as remaining seizure-free for more than 5 years.
Continuous variables are rounded to the second decimal place.

alone and were included in the seizure-persist group.

Furthermore, the clinical characteristics of patients in each treatment group were compared between the seizure-free-for-1-year and remained-seizure-free groups (Table 3). No significant differences in clinical characteristics were observed between the groups. Most patients treated with R-ES had a structural etiology in both groups; among them, a large proportion of patients were diagnosed with MCD (58.9% of the R-ES group).

EEG changes in the seizure-free groups after treatment

Both the seizure-free-for-1-year and remained-seizure-free groups showed significant improvement in EEG findings following treatment ($p < 0.001$) (Figure 2). In particular, the proportion of patients with EEG findings of 'multifocal sharp wave discharges with GSSW discharges and GPFAs' was significantly reduced after treatment. In addition, the improvement in EEG findings was significant in both the seizure-free-for-1-year and remained-seizure-free groups ($p < 0.001$). EEG findings after treatment were significantly improved in both the seizure-free-for-1-year group and the remained seizure-free group compared with the seizure-persist group ($p < 0.001$ and $p < 0.001$, respectively). The difference in the distribution of EEG findings after treatment in the seizure-free-for-1-year and remained-seizure-free groups was not significant ($p = 0.702$).

Changes in the neuropsychological status in seizure-free groups after treatment

The neurodevelopmental status was evaluated in 260 patients (Figure 3). In the seizure-free-for-1-year group, patients showed a significant improvement in neurodevelopmental status following treatment ($p < 0.001$). Among the 48 patients in the remained-seizure-free group who underwent neuropsychological evaluation, the proportion of patients with 'severe/profound ID' was significantly reduced after treatment ($p = 0.017$). However, in the seizure-persist group, there was no significant change in the neurodevelopmental status after treatment.

Discussion

This retrospective cohort study provided long-term follow-up data summarizing the treatment outcomes in patients with LGS who received various relatively consistent stepwise treatments, including ASMs, DT, and epilepsy surgery. To the best of our knowledge, our study enrolled the largest number of patients with LGS to date. We evaluated the seizure-free rate 1 year and 5 years after each treatment and assessed whether there was a significant improvement in the EEG findings and neurodevelopmental status. We observed that patients with LGS could achieve dramatic

Table 3. Comparison of clinical factors among the treatment groups according to seizure-free duration.

	Seizure-free-for-1-year group ($n=168$)[a]				Remained-seizure-free group ($n=61$)			
	ASMs	Dietary therapy	R-ES	P-ES	ASMs	Dietary therapy	R-ES	P-ES
	($n=41$)	($n=53$)	($n=56$)	($n=29$)	($n=15$)	($n=15$)	($n=19$)	($n=12$)
Age at seizure onset (years), median (range)	2.0 (0–7.0)	1.4 (0.1–9.0)	1.0 (0–10.0)	1.3 (0.1–12.0)	2.0 (0.1–5.6)	1.0 (0.3–5.0)	0.9 (0–7.0)	1.1 (0.1–12.0)
Early onset seizure (before 2 years of age), *n* (%)	20 (48.8)	29 (54.7)	34 (60.7)	17 (58.6)	7 (46.7)	9 (60.0)	11 (57.9)	8 (66.7)
History of infantile spasms, *n* (%)	10 (24.4)	15 (28.3)	18 (32.1)	12 (41.4)	3 (20.0)	4 (26.7)	8 (42.1)	4 (33.3)
Seizure type, *n* (%)								
Generalized tonic (tonic-clonic, clonic)	41 (100)	53 (100)	56 (100)	29 (100)	15 (100)	15 (100)	19 (100)	12 (100)
Myoclonic	15 (36.6)	17 (32.1)	21 (37.5)	13 (44.8)	6 (40.0)	1 (6.7)	7 (36.8)	7 (58.3)
Drop attack	16 (39.0)	17 (32.1)	16 (28.6)	10 (34.5)	7 (46.7)	5 (33.3)	4 (21.1)	5 (41.7)
Atonic	3 (7.3)	3 (5.7)	7 (12.5)	7 (24.1)	1 (6.7)	0	2 (10.5)	4 (33.3)
Atypical absence	7 (17.7)	2 (3.8)	2 (3.6)	1 (3.4)	1 (6.7)	1 (6.7)	2 (10.5)	0
Focal	7 (17.1)	10 (18.9)	14 (25.0)	8 (27.6)	5 (33.3)	4 (26.7)	5 (26.3)	2 (16.7)
Etiology, *n* (%)								
Structural, *n* (%)	14 (34.1)	21 (39.6)	53 (94.6)	15 (51.7)	6 (40.0)	6 (40.0)	19 (100)	5 (41.7)
Destructive	10 (24.4)	13 (24.5)	15 (26.8)	4 (13.8)	4 (26.7)	5 (33.3)	5 (26.3)	2 (16.7)
MCD	4 (9.8)	8 (15.1)	33 (58.9)	8 (27.6)	2 (13.3)	1 (6.7)	14 (73.7)	3 (25.0)
FCD	1 (2.4)	3 (5.7)	11 (19.6)	3 (10.3)	1 (6.7)	1 (6.7)	4 (21.1)	1 (8.3)
Non-FCD	3 (7.3)	5 (9.4)	22 (39.3)	5 (17.2)	1 (6.7)	0	10 (52.6)	2 (16.7)
Gliosis alone	0	0	5 (8.9)	3 (10.3)	0	0	1 (5.3)	0
Genetic, *n* (%)	2 (4.9)	7 (13.2)	0	1 (3.4)	2 (13.3)	3 (20.0)	0	1 (8.3)
Unknown, *n* (%)	25 (61.0)	25 (47.2)	0	13 (44.8)	7 (46.7)	6 (40.0)	0	6 (50.0)
Number of ASMs ever used, median (range)	4.0 (2.0–7.0)	5.0 (2.0–9.0)	4.0 (2.0–10.0)	4.0 (2.0–9.0)	4.0 (2.0–6.0)	5.0 (2.0–6.0)	6.0 (2.0–9.0)	4.5 (2.0–9.0)

'Remained-seizure-free' was defined as remaining seizure-free for more than 5 years.
ASMs, antiseizure medications; FCD, focal cortical dysplasia; MCD, malformation of cortical development; P-ES, palliative epilepsy surgery; R-ES, resective epilepsy surgery.
Data are presented as median (range) for continuous variables and number (%) for categorical variables. The chi-square test and Fisher's exact test were used for categorical variables, as appropriate.
Continuous variables are rounded to the second decimal place.
[a]Eleven patients who underwent P-ES because of seizure relapse after R-ES were not counted in duplicate.

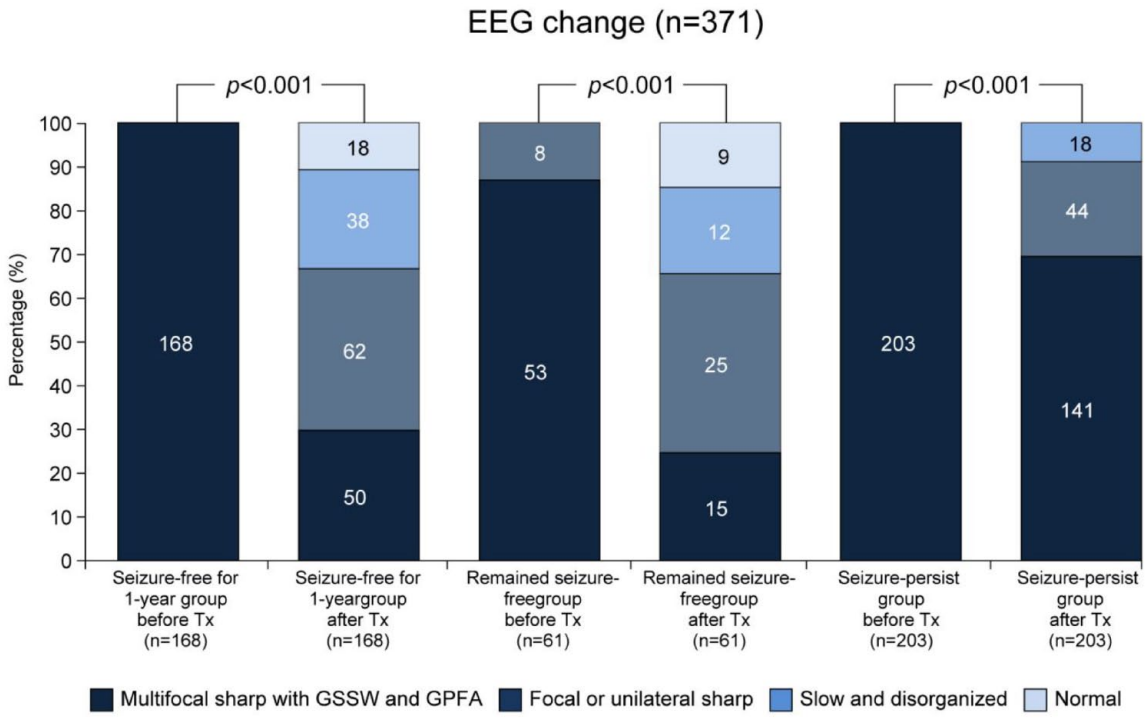

Figure 2. Differences in electroencephalogram findings in patients with LGS before and after treatment.
GPFA, generalized paroxysmal fast activity; GSSW, generalized slow spike and wave; LGS, Lennox-Gastaut syndrome; Tx, treatment.

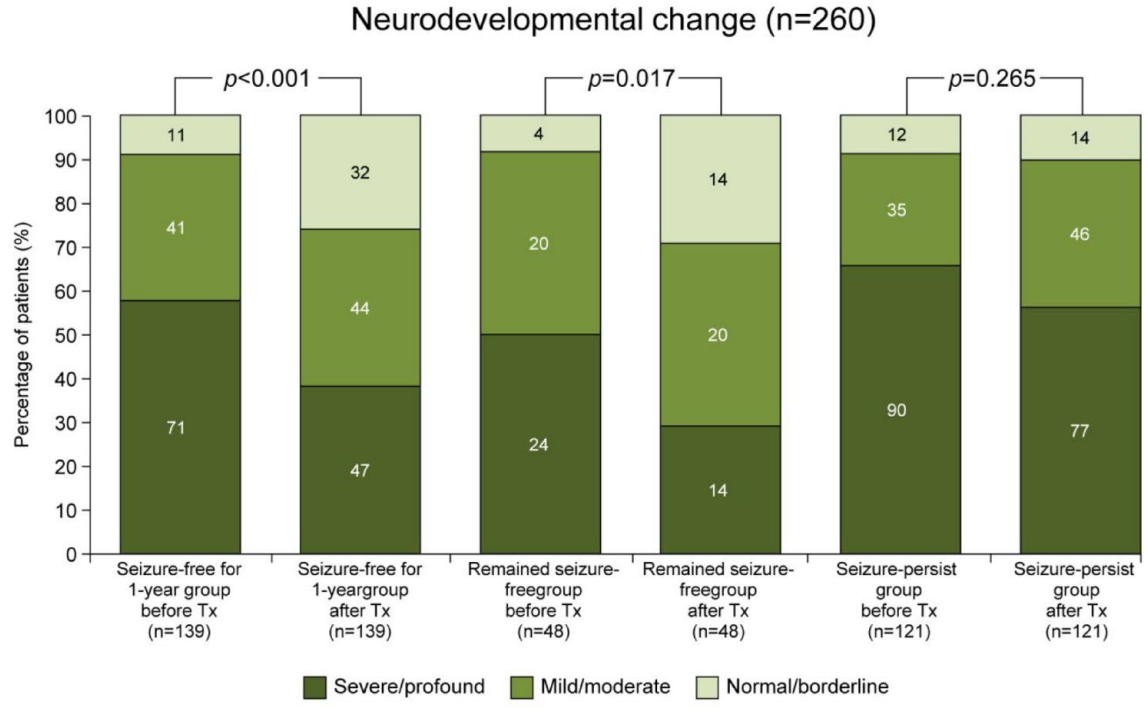

Figure 3. Differences in the neurodevelopmental status in patients with LGS before and after treatment.
LGS, Lennox-Gastaut syndrome; Tx, treatment.

improvement in the seizures and neurodevelopmental status if they actively undergo multidisciplinary treatment.

In children, seizure freedom is the main goal of epilepsy treatment to preserve the neurodevelopmental function, irrespective of the epileptic syndrome. The seizure-free rate could be used as a measure of treatment success in patients with LGS.[6,8] At present, the available unimodal treatments are less likely to lead to seizure freedom in most patients with LGS.[15] The seizure-free rate in patients with LGS who receive ASMs alone is reportedly less than 10%.[20,21] In our study, we observed that 11.1% of patients with LGS who received ASMs remained seizure-free for 1 year, while 4.1% remained seizure-free for more than 5 years. Moreover, our study showed that multimodal treatment strategies had a comparatively higher rate of seizure-free outcomes; in our study, 168/371 (45.3%) patients with LGS who underwent multimodal therapy were seizure-free for 1 year, including 61/371 (16.4%) patients who remained seizure-free for more than 5 years. Among those treated using DT, 26.4% remained seizure-free for 1 year and 7.5% remained seizure-free for 5 years or more. In addition, when epilepsy surgery was further applied for treatment, 50.0% and 17.0% of patients who underwent R-ES and 25.2% and 10.4% of patients who underwent P-ES remained seizure-free for 1 year and 5 years, respectively. This emphasizes that our long-term follow-up and treatment data are worth referencing in the future. Moreover, the active application of multimodal treatment may result in a high success rate in patients with LGS.[6,8,10,22]

DT may be considered appropriate for patients with LGS who do not respond to treatment with multiple ASMs. In previous studies, DT has been reported to lead to a seizure-free outcome, the rate of which exceeds that of ASM treatment alone. In our study, the seizure-free rate following DT was more than twice compared with that observed following ASM treatment alone.[6,20,23] In addition, DT could be initiated early in patients with LGS with symptomatic etiologies (metabolic or genetic causes), as well as surgery-eligible structural brain abnormalities. The side effects of DT can generally be resolved, and DT can be flexibly applied as a classical KD, MAD, or LGI diet, among others, depending on the ability of patients with LGS to tolerate DT.[10,19] DT has antiepileptic and neuroprotective effects, and long-term application of DT increases mitochondrial function and improves cognitive function.[23,24] In addition, in patients with LGS who are considered for surgical treatment, DT should be actively attempted before epilepsy surgery. However, as the patient's ability to tolerate DT is an obstacle to the long-term application of this therapy, strategies to improve the tolerability of DT should be developed.

Epilepsy surgery is a powerful treatment approach that can lead to a seizure-free status in patients with LGS. When focality is present, the patients are eligible for R-ES, which reportedly leads to the best seizure-free outcomes. Among the different forms of P-ES, CC is associated with relatively good seizure-free outcomes through efficient alteration of the brain network topology. Epilepsy surgery should be actively considered for patients with LGS refractory to ASMs and DT.[6,8,13,25] In our study, R-ES was mainly performed when MCD was identified as the etiology based on MRI findings; however, R-ES could be effectively performed even in the presence of destructive lesions. In addition, R-ES and CC led to significantly higher seizure-free outcomes than ASM treatment and DT. In particular, hemispherectomy had the highest seizure-free rate among all treatment methods (seizure-free for 1 year, 52%; remained seizure-free, 24%) and should be considered for eligible patients. Furthermore, multilobar resection also showed a high rate of seizure-free outcomes, suggesting that this could be a suitable surgical treatment for patients with LGS. However, despite the increasing need for epileptic surgery in pediatric patients with intractable epilepsy, there are barriers to the sufficient use of epileptic surgery in practice such as negative attitudes about epilepsy surgery, lack of epilepsy surgery centers, and lack of improved diagnostic tools to delineate the extent of the epileptogenic zone.[26] Therefore, the accessibility of surgery must be improved through the development of new technologies for epilepsy surgery based on specific network contributions, as well as through the resolution of misconceptions regarding epilepsy surgery and improvement in the healthcare system.[26,27]

We observed that the active application of multimodal treatment led to significant improvements in the EEG findings and neurodevelopmental status, as well as seizure-free outcomes, in patients with LGS. Improvements in severe EEG

abnormalities, including GSSW discharges and GPFAs, suggest that the treatment is effective; furthermore, desirable progress is observed in the long-term neurodevelopmental status.[8,16] In our study, improvements in severe EEG abnormalities were observed in both the seizure-free and seizure-persist groups. Given that the ultimate goal of treating pediatric epilepsy is the normalization of neurodevelopmental status, the importance of multimodal treatment is further emphasized.

This study provides updated clinical evidence of long-term seizure-free outcomes and neurodevelopmental improvements in a large cohort of patients with LGS following the active application of comprehensive multimodal treatments, such as ASMs, DT, and surgery. We emphasize that compared with unimodal treatment, actively combining multiple ASMs, DT, and surgical treatment could significantly improve short-term and long-term seizure-free outcomes, thus benefiting the neurodevelopmental progress of patients with LGS. However, our study has some limitations. First, the inherent limitations of the retrospective study design might have compromised the accuracy of the collected data. Second, in our study, known genetic etiologies alone were evaluated, and information on emerging genetic etiologies is lacking.[5] Third, information on patients lost to follow-up or those who refused additional treatment was insufficient. Nevertheless, this study provided a comprehensive description of clinical variables in patients with LGS and the long-term treatment outcomes of relatively consistent multimodal treatment methods for treating this devastating epilepsy syndrome. We emphasize that active application of multimodal treatment for LGS patients can improve not only their seizure outcome but also their quality of life. Because of the limitation that this study is not a sequential trial study design, our data might be inconclusive and limited regarding the information on the best treatment options. However, our results are highly informative to many epileptologists and could be used as an important reference in future studies regarding LGS. Although conducting large randomized controlled trials on treatment modalities for patients with LGS is not feasible, studies on treatment protocols tailored to a specific etiology should be conducted. In the future, we will continue to explore novel and effective treatment options for patients with LGS. Moreover, further studies on emerging treatment methods for LGS are also needed to increase the efficiency of the multimodal approach.[11,28]

Declarations

Ethics statement

This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine (4-2020-1204)., which waived the requirement for informed consent for this study. 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.

Consent for publication

We declare that all authors consent the publication of the presented manuscript.

Author contributions

Ji-Hoon Na: Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Da Eun Jung: Formal analysis; Validation; Writing – review & editing.

Hee Jung Kang: Data curation.

Hoon-Chul Kang: Data curation; Resources; Supervision; Validation.

Heung Dong Kim: Conceptualization; Funding acquisition; Methodology; Resources; Supervision; Writing – review & editing.

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Conflict of interest statement

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Availability of data and materials

Further information and requests for data and materials should be directed to the corresponding

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