Long term outcome of Lennox-Gastaut syndrome

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ABSTRACT

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I performed a long-term follow-up study in patients with Lennox-Gastaut syndrome (LGS). Sixty-eight patients that were more than 18 years of age were included in this study. The type of seizure, seizure frequency, electroencephalography (EEG) characteristics, cognitive function, motor disability, treatment and seizure outcomes were evaluated. Patients were aged 18.7 to 35.8 years (mean 23.0 years) and the follow-up duration ranged from 8.3 to 32.5 years (mean 19.3 years). Seizures and EEGs changed with age. Although the seizure frequency and intensity decreased, 76.5% of the patients sustained seizures, which were mainly generalized tonic, atonic or generalized tonic-clonic seizures. The age at seizure onset, etiology, brain magnetic resonance imaging (MRI) abnormalities and history of infantile spasms were not associated with seizure outcomes. Characteristic EEG features of diffuse slow spike-wave (DSSW) and generalized paroxysmal fast activities (GPFA) disappeared in half of the patients. In regards to cognitive function, 94.7% of the patients exhibited moderate to profound mental retardation that was independent of many clinical factors or seizure outcomes. Only 39.7% of the patients had independent daily living skills and 25.4% could not walk even with support. Although LGS is a form of intractable epilepsy, applying diverse treatments including ketogenic diet and surgeries to the patients that have had other unsuccessful treatments can lead to more successful seizure control.

Key words: Lennox-Gastaut syndrome, long term follow up, seizure outcome

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I. INTRODUCTION

Lennox-Gastaut syndrome (LGS) is a severe childhood-onset epileptic encephalopathy that is characterized by multiple types of seizures, progressive mental retardation and an interictal electroencephalographic pattern of diffuse slow spike-wave (DSSW) complexes while awake and generalized paroxysmal fast activities (GPFA) during sleep.[1,2] LGS usually begins before 8 years of age, peaks between 3 and 5 years, and it accounts for approximately 1-4% of childhood epilepsies.[3] Previous studies commonly reported that the LGS prognosis was poor.[4,5,6] Roger *et al*. followed 338 LGS patients until adulthood, and determined that 62.4% of the patients had unfavorable outcomes.[4] A long-term follow-up study of 89 patients with LGS by Ohtsuka *et al*. showed persistent seizures in 76.4% of the patients who were followed for more than five years.[5] Oguni *et al*. reported that more than two thirds of 72 patients with LGS who were followed for more than 10 years showed persistent daily or weekly seizures.[6] LGS is one of the most difficult forms of epilepsy to treat. Therapy is complicated by multiple seizure types, intractability and adverse polypharmacy effects, among other things. Nevertheless, various treatment options have been applied including antiepileptic drug (AED) medications, a

ketogenic diet (KD) and epilepsy surgery. Each treatment has been effective for reducing seizure frequency, however long-term follow up has never been reported.

This study investigated overall seizure outcomes, cognitive function and independent daily living abilities of adult patients with LGS. Correlations between many clinical factors and final outcomes were surveyed. I also tried to assess the evolution of clinical and electroencephalographic characteristics.

Ⅱ. PATIENTS AND METHODS

I reviewed medical records of follow-up patients from Severance Children's Hospital diagnosed with LGS that were more than 18 years of age. The following criteria were used to diagnose LGS: multiple types of seizures, interictal DSSW, and cognitive impairment. All patients were retrospectively evaluated with regard to etiology, electroencephalography (EEG), seizure types, frequency of seizures, antiepileptic treatment and other treatments, response to therapies, cognitive function and seizure outcomes. Additional clinical data including age, gender, follow-up duration, age of seizure onset, history of infantile spasms, brain magnetic resonance imaging (MRI), comorbidities, possibility of ambulation, possibility of independent daily life, and past history of perinatal asphyxia, head trauma and encephalitis were obtained from medical records. The etiology of LGS was divided into a cryptogenic group and a symptomatic group. The cryptogenic group included patients with no abnormal neurological signs and no preceding developmental delay before seizure onset, and who showed no abnormal findings on neuroimaging, genetic, and metabolic evaluations. Patients who had developed neurologic dysfunction before seizure onset and showed any abnormalities on neuroimaging or genetic or metabolic work-up were assigned to the symptomatic group. The symptomatic group was subdivided into three categories; malformation, destruction and patients that had genetic or metabolic causes. Initial and most recent EEGs were analyzed. I checked the presence of slow and disorganized background rhythm and characteristic EEG features such as DSSW, GPFA and multifocal independent spikes. I used the intelligence quotient (IQ) as an index of cognitive function. Neuropsychological assessments were performed in 56 patients by psychologists. IQ was assessed by the Korean-Wechsler Intelligence Scale for Children (K-WISC) or Korean-Wechsler Adults Intelligence Scale (K-WAIS). Seizure types were classified into generalized tonic, generalized tonic-clonic,

myoclonic, atonic, atypical absence, complex partial and epileptic spasms. Seizure outcome was assessed at the most recent visit and divided into daily, weekly, monthly seizure and seizure-free categories that reflected the seizure frequencies of the past year. Responses to the each therapy were also assessed at the last visit and the patients were divided into responding or non-responding groups. If the frequency of main seizures was reduced by more than 50%, the patient was designated as responding. Engel's classification[7] was also assessed in cases of surgery. The R package version 3.0.1 was used for statistical poisson regression and logistic regression. $P<0.05$ was regarded as statistically significant.

Ⅲ. RESULTS

1. Clinical Profiles

A total of 68 patients (42 male and 26 female) who fulfilled LGS diagnostic criteria that were older than 18 years were identified (Table 1). The mean age was 23.0 ± 3.8 years (range, 18.7 to 35.8 years) and the mean follow-up duration was 19.3 ± 6.0 years (range, 8.3 to 32.5 years). Age of seizure onset ranged from 1 month to 13 years (mean, 44.7 ± 46.1 months); under 12 months in 35.3%, between 12 and 60 months in 33.8% and older than 60 months in 30.9%. Sixteen patients (23.5%) had a history of infantile spasms. Brain MRI was normal in 22 patients (32.4%), there was atrophy only, in 11 patients (16.2%) and there were 34 patients with other abnormal tests (50.0%). The etiology of LGS was estimated from past history, brain MRI and genetic studies. Forty-six patients (67.6%) were symptomatic and 22 patients (32.4%) were cryptogenic (Table 2). Among the symptomatic group, 18 patients (26.5%) had a malformed brain, in which focal cortical dysplasia, other cortical dysplasia such as lissencephaly, band heterotopia, polymicrogyria and porencephaly, tuber in tuberous sclerosis, hypothalamic hamartoma and cavernous hemangioma were included. Sixteen patients (23.5%) had a damaged brain, which included hypoxic encephalopathy, head trauma, infarction and sequelae of meningitis or encephalitis. Twelve patients (17.6%) had genetic or metabolic causes, which included Down syndrome, Rett syndrome and mitochondrial disease.

Table1. Clinical profiles

Characteristics	Values
Age, years	23.0±3.8 (18.7-35.8)
Gender (male:female), n	42:26
Follow-up duration, years	19.3±6.0 (8.3-32.5)
Age of seizure onset, months	44.7±46.1
<12 months, n (%)	24 (35.3)
12-60 months, n (%)	23 (33.8)
>60 months, n (%)	21 (30.9)
Brain MRI, n (%)	
Normal	22 (32.4)
Atrophy only	11 (16.2)
Abnormal	34 (50.0)
History of infantile spasms, n (%)	16 (23.5)

MRI, magnetic resonance imaging

Table 2. Etiology

Etiology	n (%)
Symptomatic	46 (67.6%)
Malformation[1]	18 (26.5%)
Destruction[2]	16 (23.5%)
Metabolic or genetic[3]	12 (17.6%)
Cryptogenic	22 (32.4%)

[1]focal cortical dysplasia, lissencephaly, band heterotopia, polymicrogyria, porencephaly, tumor, tuber

[2] hypoxic encephalopathy, infection, head trauma, infarction

[3] chromosomal or genetic abnormality, mitochondrial disease

2. Cognitive function and activities of daily living

Among 68 patients, 56 patients were evaluated with a neuropsychological test. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) classification[8], 94.7% of the patients had moderate to profound mental retardation (Table 3). Correlations between the symptomatic group in etiology (1.098, p=0.537), seizure onset age (0.999, p=0.720), history of infantile spasms (1.099, p=0.553), brain MRI abnormalities (1.018, p=0.905) and IQ were not significant.

Ability of ambulation or activities of daily living (ADL) could be evaluated in 63 patients. Ambulation was possible in 46 patients (74.6%) with or without support and not possible in 16 patients (25.4%). Independent daily living skills, including eating, bathing, toileting and transferring were possible in 25 patients (39.7%) and not possible in 38 patients (60.3%). Correlations between symptomatic etiology, age of seizure onset, history of infantile spasms, brain MRI abnormalities and ambulation or activities of daily living were evaluated (Table 4). Age of seizure onset showed nearly no impact on ambulation or ADL. The possibility of ambulation was 4.7 times higher (p=0.055) in the cryptogenic group and ADL was 4.1 times higher (p=0.013) than in the symptomatic group. Patients who had no history of infantile spasms were 1.2 times (p=0.757) and 1.9 times (p=0.340) more likely to have ambulation and ADL, respectively, than patients who had infantile spasms. Furthermore, patients with normal brain MRI scans were 2.7 times (p=0.170) and 2.5 times (p=0.105) more likely to have ambulation and ADL, respectively, than patients with an abnormal brain MRI. However, only the relationship between etiology and ADL was statistically significant.

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Table 3. Cognitive function (n=56)

IQ	n (%)
Normal (IQ>85)	0 (0)
Borderline (70<IQ<85)	2 (3.6)
Mild MR (50~55<IQ<70)	1 (1.8)
Moderate MR (35~40 <IQ<50~55)	9 (16.1)
Severe MR (20~25<IQ<35~40)	30 (53.6)
Profound MR (IQ<20~25)	14 (25.0)

MR, mental retardation; IQ, intelligence quotient

Table 4. Clinical factors and ambulation or ADL correlations

variable	ambulation		ADL	
	OR	p-value	OR	p-value
Seizure onset age (months)	1.010	0.188	1.009	0.097
Symptomatic etiology	0.211	0.055	0.246	0.013*
History of infantile spasms	0.811	0.757	0.533	0.340
Abnormal brain MRI	0.367	0.170	0.393	0.105

ADL, activities of daily living; OR, Odds Ratio; MRI, magnetic resonance imaging

3. Evolution of seizure types and EEG

The types of seizures were observed in 68 patients throughout the clinical course, and consisted of generalized tonic seizures in 97.1%, myoclonic seizures in 52.9%, atonic seizures in 50.0%, generalized tonic-clonic seizures in 35.3%, atypical absence seizures in 25.0%, spasms in 23.5%, complex partial seizures in 22.1%, status epilepticus in 19.1% and gelastic seizures in 1.5% (Fig.1). Gelastic seizures were found in one patient who had hypothalamic hamartoma. At the last visit, 39.7% of the patients had generalized tonic seizures, 22.1% had atonic seizures, 13.2% had generalized tonic-clonic seizures, 11.8% had myoclonic seizures, 5% had complex partial seizures and 1.5% had atypical absence seizures. Spasms or status epilepticus were not reported in any patient at the last visit (Fig.1).

At the initial visit, the EEG of all patients showed slow and disorganized background rhythm. Additionally, 94.1% of the patients showed DSSW, 48.5% showed GPFA, 60.3% showed multifocal spikes and 10.3% showed solitary spikes. At the most recent observation, 80.9% of the patients presented with slow and disorganized background rhythm, 41.2% and 22.1% still presented with DSSW and GPFA, respectively, 29.4% presented with multifocal spikes and 35.3% presented with solitary spikes (Fig.2). Eight patients (11.8%) showed normal EEG patterns at their last visit.

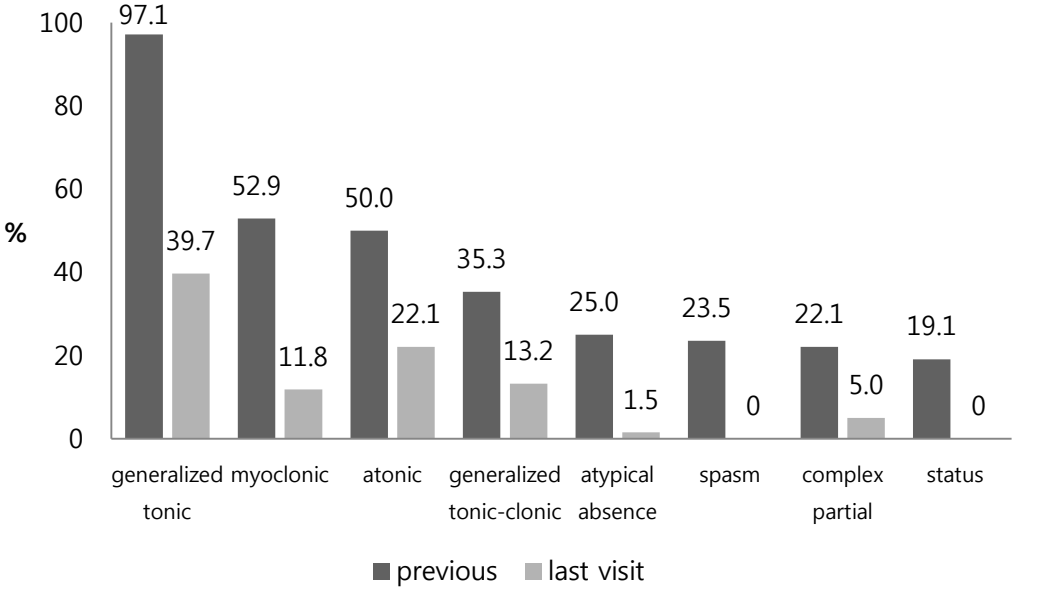

Fig.1. Evolution of seizure types

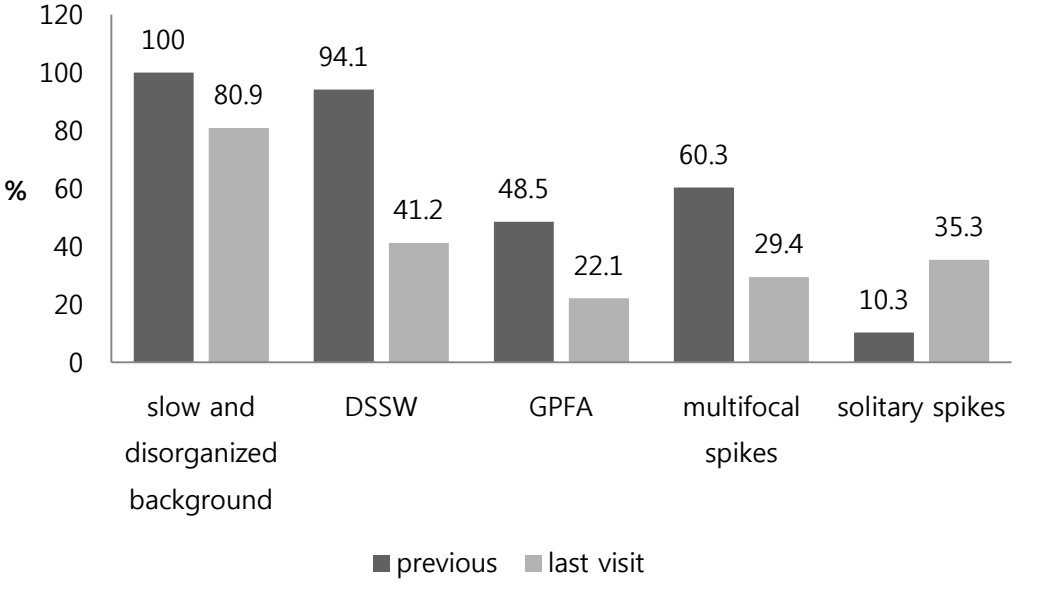

Fig.2. Evolution of EEG

4. Treatments and seizure outcomes

Of the 68 patients, all the patients had taken AEDs. Twenty-six patients (38.2%) were treated only with AEDs and without other treatments. Among the 26 patients, six patients became seizure-free. Forty-two (61.8%) patients were treated with AEDs and additional treatment modalities. Nineteen patients were given applied KD, and among these, two patients became seizure free, 14 patients underwent epilepsy surgery and the other three patients had persistent seizures without surgery. In comparison, 23 patients had epilepsy surgery without KD. A total of 37 patients had epilepsy surgeries and 10 of the 37 patients had two or more surgeries. Vagus nerve stimulation (VNS) was performed in 14 patients, corpus callosotomy (CC) was performed in 17 patients and resective surgery was performed in 18 patients. After surgery, eight patients became seizure-free: five from resective surgery, two from CC and one from VNS (Fig. 3A). To summarize the responses according to the number of treatment modalities, five patients became seizure free after one surgery without diet therapy: three from resection, one from CC and one from VNS (Fig. 3B). Three patients became seizure-free after KD and additional surgeries (Fig. 3B). The patients who were treated with AEDs and two or more additional treatments are summarized in Table 4. Two patients became seizure free after KD and one surgery: CC and resection respectively. The patient (patient 5) who underwent KD and CC had diffuse hypoxic brain damage after status epilepticus at the age of four. At the age of 13, daily head nodding and atypical absence seizures persisted despite KD, therefore, the patient underwent CC. After CC and with KD maintained, the seizure frequency was decreased to monthly seizures and the patient became seizure-free at 20 years. The patient (patient 12) who had KD and resection had infantile spasms at 3-months old, due to cortical dysplasia. After KD, he had been seizure-free for five years, but then the seizures recurred. At 13 years, he underwent resection of the left frontal

lobe. After surgery, he had been seizure free without medication and his EEG also became normal. One patient (patient 17) became seizure-free after KD and two resective surgeries. He experienced his first seizure at 9-years old due to cortical dysplasia. His KD was intolerable and he had a resection of the right temporal lobe at 13 years of age. After surgery, he had been seizure-free for three months, however, his seizure recurred and reevaluation confirmed incomplete resection. He underwent residual resection of the right temporal lobe at 16 years and became seizure-free with maintenance AEDs.

Patients treated with AEDs and two or more additional treatments, summarized in Table 4, had more intractable seizures than the patients treated with one or two treatment modalities. Among the 18 patients with intractable seizures, the final seizure outcome was observed in the last visit. This observation indicated that 10 patients (55.6%) presented with improvement with Engel class I to III, whereas 8 patients (44.4%) presented without improvement with Engel class IV (Table 5). To assess the response to each therapy, the patients were divided into responding or non-responding groups based on the last visit, and the response rate of each treatment was as follows: fifty percent in resection, 29.4% in CC, 28.6% in VNS and 31.6% in KD (Table 6).

All the patients were treated with AEDs. Throughout the treatment course, valproic acid was used most frequently (88.2%), followed by lamotrigine (66.2%), zonisamide (50.0%), vigabatrin (50.0%) and levetiracetam (47.1%). Topiramate (42.6%), rufinamide (39.7%), clobazam (32.4%), phenobarbital (30.9%) and clonazepam (29.4%) were also frequently used (Fig 4). At the last visit, valproic acid (75%) was still the most frequently used, followed by lamotrigine (54.4%), levetiracetam (42.6%), zonisamide (36.8%), rufinamide (33.8%) and topiramate (32.4%) (Fig. 4).

Final seizure outcomes, evaluated at the last visit according to the frequency of main seizure types were as follows. Sixteen patients (23.5%) were seizure-free, monthly seizures occurred in 18 patients (26.5%), weekly seizures in 13 patients

(19.1%) and daily seizures in 21 patients (30.9%) (Fig. 5). Statistical analysis of clinical factors including seizure onset age, etiology, history of infantile spasms, brain MRI abnormalities, IQ, ambulation, and ADL, that could affect the final seizure frequency were not significant.

From 8.3 to 32.5 years of follow-up, 16 patients became seizure-free. Time from seizure onset to seizure-free status ranged from 68 months to 288 months. A Kaplan-Meier plot for seizure-free patients was obtained (Fig. 6).

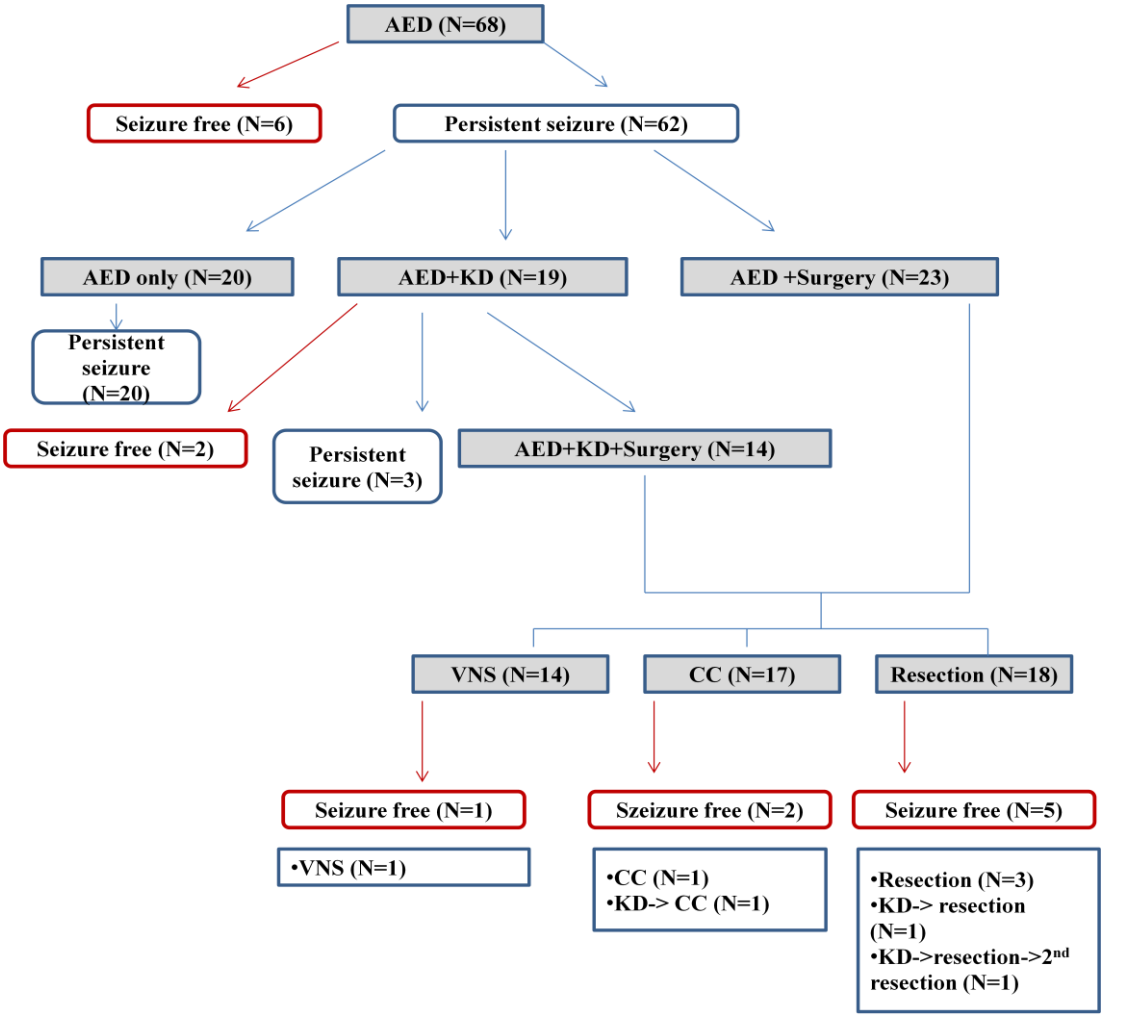

Fig.3A. Treatments and responses flow chart

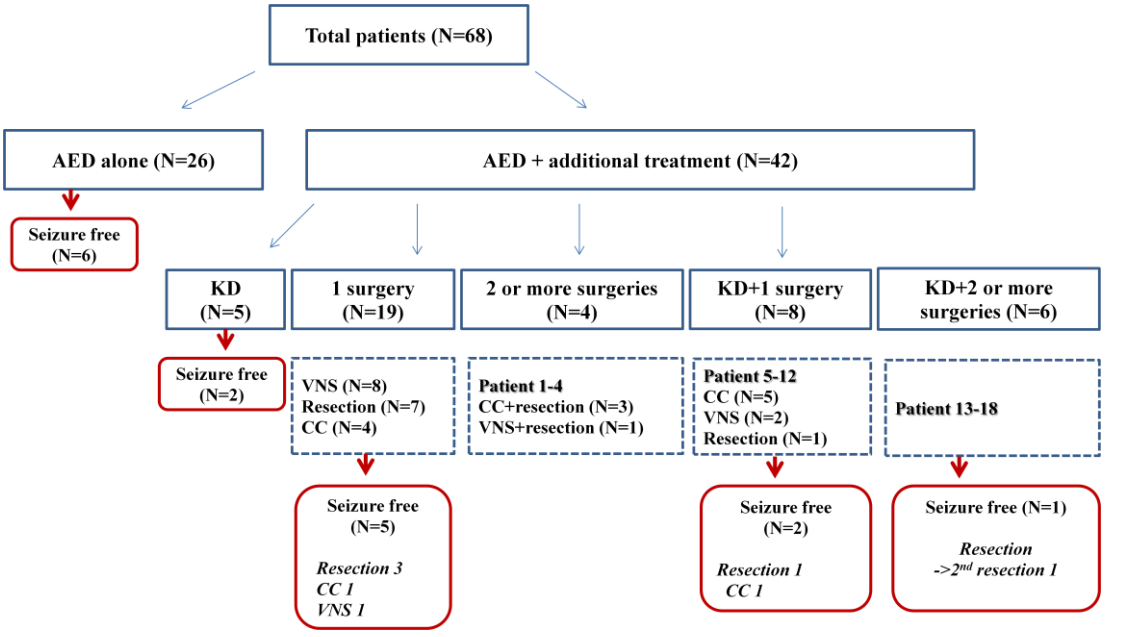

Fig.3B. Treatments and responses flow chart

Table 5. AED and two or more additional treatments

Patient		Last seizure frequency	Engel's class
1	VNS→VNS removal→hamartoma resection→2nd hamartoma resection	daily	IV
2	resection→CC	weekly	III
3	CC→resection	monthly	II
4	CC→resection	daily	IV
5	KD→CC	sz free	I
6	KD→CC	monthly	II
7	KD→CC	monthly	II
8	KD→CC	daily	IV
9	KD→CC	monthly	I
10	KD→VNS	weekly	III
11	KD→VNS	daily	IV
12	KD→resection	sz free	I
13	KD→VNS→CC	weekly	III
14	KD→CC→VNS	daily	IV
15	KD→CC→resection	daily	IV
16	KD→resection→CC	daily	IV
17	KD→resection→2nd resection	sz free	I
18	KD→CC→VNS→resection	daily	IV

AED, antiepileptic drug; VNS, vagus nerve stimulation; CC, corpus callosotomy; KD, ketogenic diet

Table 6. Treatment response rates

	n	%	Follow-up duration (months)
VNS	4/14	28.6	63.7±30.1
CC	5/17	29.4	72.8±47.0
Resection	9/18	50.0	58.8±26.5
KD	6/19	31.6	

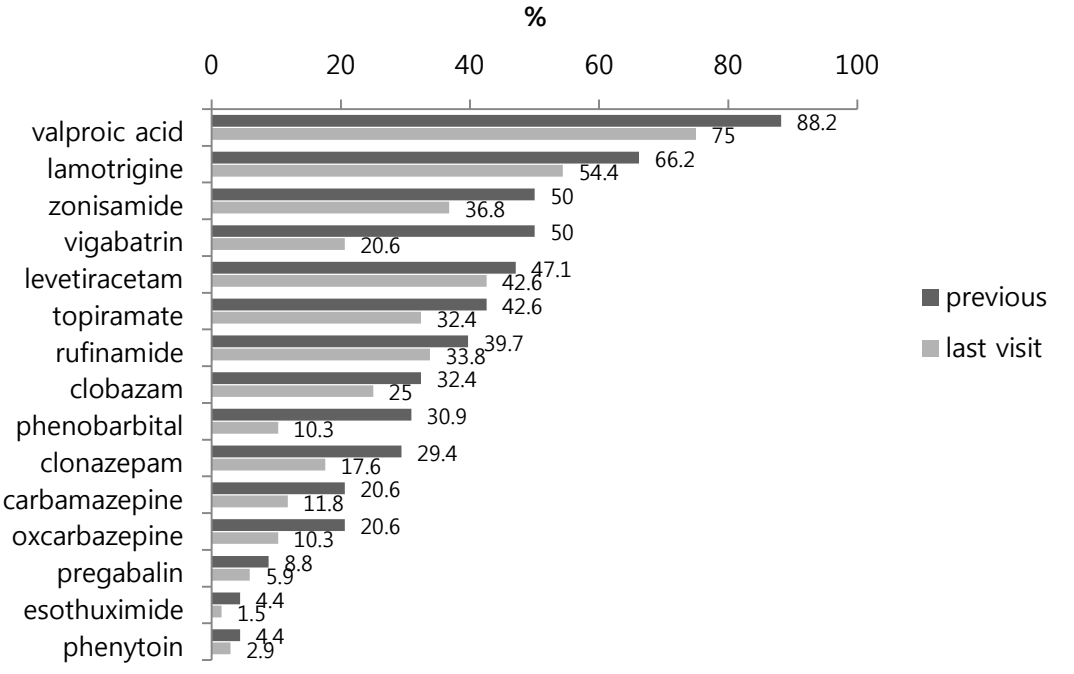

Fig.4. Antiepileptic medications

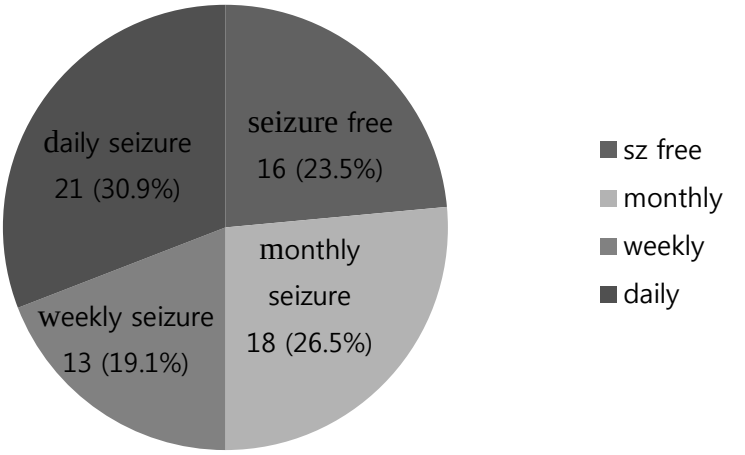

Fig.5. Last seizure frequency of main seizure type

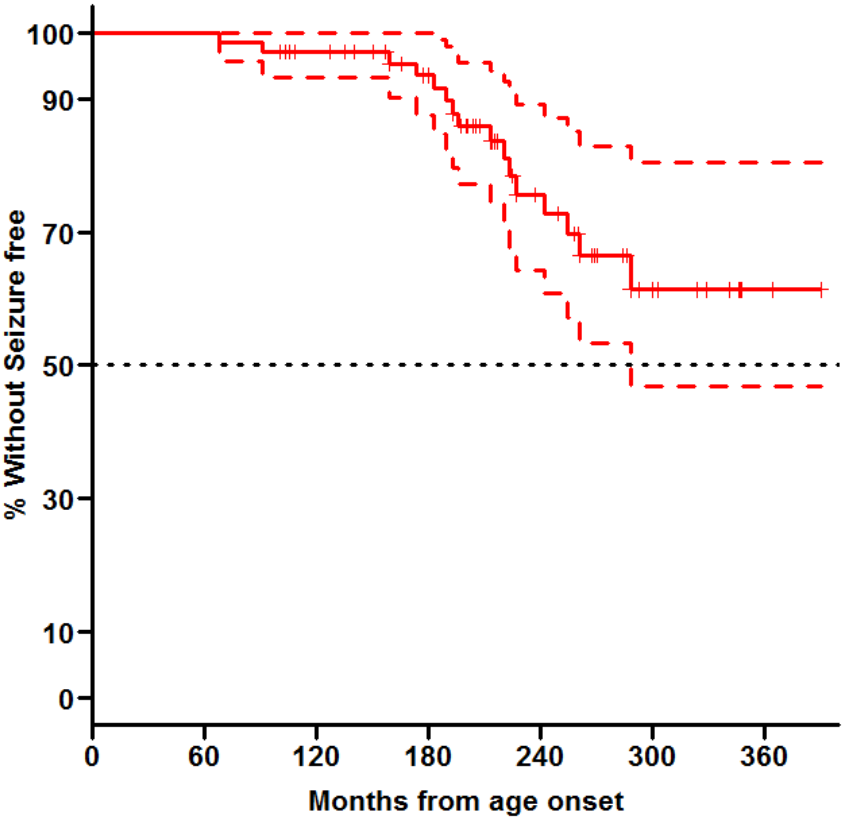

Fig.6. Kaplan-Meier seizure free plot

IV. DISCUSSION

In this study I observed 68 patients with LGS that were 18 years of age or older, and 76.5% of the patients had persistent seizures despite aggressive treatment. However, as presented in the Kaplan-Meier plot, the number of seizure-free patients increased with the increase in age. Seizure frequency and intensity decreased in adult patients and types of seizures and EEG characteristics also changed.

In this study, generalized tonic seizures and atonic seizures were frequent in adult patients, while myoclonic seizures and atypical absence seizures were markedly decreased. This finding is consistent with previous results. Ohtsuka *et al*. described tonic spasms as the most difficult seizure to control. Yagi observed 102 patients with LGS for more than 10 years, and found persistent generalized tonic seizures in nearly all patients.[9] Ferlazzo *et al*. studied 27 LGS patients aged 40-59 years, and concluded that tonic seizures during sleep remained the major type of seizure.[10]

The EEG changes revealed that DSSW, GPFA and multifocal spikes disappeared in half of the patients, while background slowing was sustained in 80% of the patients and solitary spikes increased. Previous studies showed similar findings. DSSW specific to LGS gradually disappeared and EEG was replaced by multifocal independent spikes.[5,6] This phenomenon is because GSSW is produced by subcortical level structures, and when the brain cortex matures, GSSW is suppressed and focal cortical discharges gain dominance.[5,6] Yagi analyzed the evolution of EEG in LGS. At first, DSSW disappeared while GPFA and multifocal spikes remained; next GPFA disappeared and finally multifocal spikes decreased and disappeared.[9] Another study insisted that multifocal independent spikes are intermediate between hypsarrhythmia and GSSW.[11] However, in that study, the patients were less than 10 years of age which could affect the comparison. Therefore, EEG changes in the older age

groups were not observed. Ferlazzo *et al*. observed that in older patients aged 40-59 years, 55% showed abnormal background activities, GSSW was identified in 26% and focal epileptic abnormalities were identified in 30%, whereas almost all patients retained GPFA during sleep.[10]

Typical LGS feature changes were documented and half of the patients in this study aged 18.7-35.8 years still sustained daily or weekly seizures although the seizures were less intense. I investigated clinical factors that influenced seizure outcomes including seizure onset age, etiology, brain MRI abnormalities, history of infantile spasms, and IQ. However, I did not identify specific correlations between each factor and seizure outcomes. I also analyzed the difference of these factors in the seizure-free group and others, although the results were not statistically significant. Similar results were also found in other studies. Ohtsuka *et al*. concluded that the age of seizure onset and history of infantile spasms was not correlated with seizure prognosis.[5] Goldsmith *et al*. observed 74 patients with LGS classified into cryptogenic, intermediate and symptomatic groups, although there was no significant difference in seizure outcomes in each group.[12] Although the pathogenesis of LGS has not been clearly understood until now, common processes may work to produce seizures and affect disease progression, independent of etiology or underlying disease. Furthermore, as seizures in LGS are mostly severe, I hypothesized that seizure outcomes are more dependent on proper treatment.

Cognition impairments are characteristic of LGS. In addition to seizures, cognitive, behavioral and physical problems are also severe in LGS. Several previous studies concluded that early onset seizures, symptomatic etiology and previous infantile spasms are risk factors for severe mental retardation.[5,13] Our results, which did not indicate any significant correlation, could be affected by the severity of mental retardation. Although we could not perform serial IQ evaluations, cognitive impairment increases with age in LGS.[6] The IQ scores which were most recently evaluated in this patients were mostly severe,

therefore most patients were categorized with severe or profound mental retardation. These distributions could have affected the statistical analysis.

Physical and mental disability of LGS patients impairs the quality of life. There was an increasing tendency for ambulation difficulty in patients that had an abnormal brain MRI or symptomatic etiology, although this result was not statistically significant. Impairment of ADL, which was found in 60.3% of patients, is thought to be associated with intractable seizures, ambulation difficulty, cognitive impairment and adverse effects of AEDs. Treatment of LGS in adolescence and adulthood should focus on improving the patient's quality of life, balancing seizure control and preventing disability. LGS is an epileptic encephalopathy, which means that persistent seizures can cause mental deterioration, while polytherapy increases the risk of adverse effects. For example, Ogawa *et al*. stated that swallowing difficulty may be regarded as an important sign of the progression of epileptic encephalopathy.[14] Perucca *et al.* reported that use of benzodiazepine could precipitate tonic status epilepticus in LGS.[15] Careful efforts for effective seizure control with the fewest adverse effects and co-morbidity management are necessary.

All patients in this study were treated with AEDs. Although valproic acid was most frequently used, only five AEDs including felbamate, lamotrigine, topiramate, rufinamide and clobazam showed proven effectiveness in LGS in randomized controlled trials.[16,17,18,19,20,21] Unfortunately, I could not evaluate the efficacy of each drug for each type of seizure because of the complexity of the disease and treatments. In practice, prescribing AEDs for LGS patients is usually based on clinical experience. Differences in commonly used AEDs between previous and last visits included the use of vigabatrin and phenobarbital decreased, and the use of levetiracetam and rufinamide increased in the last visit. Finally, it is possible that resolution of infantile spasms and development of new drugs are associated with the changes.

In this study, 42 patients (61.8%) underwent 49 surgeries and 19 diet therapies. The long-term outcomes of each surgery were assessed at the last visit. However, the KD outcomes were assessed at the end of the KD, because only two patients maintained the KD at the last visit (Table 5). For example, patient 13, who had cryptogenic etiology, experienced the first seizure at age 7. She had daily generalized tonic seizures accompanied by traumatic falling and complex partial seizures. The AED treatment was ineffective and she maintained KD for 2 years. After KD, the daily generalized tonic seizures decreased to weekly seizures, however, she refused to further maintain KD due to inconvenience. After the patient discontinued KD, the seizures increased to daily seizures. At 16, she underwent VNS and daily generalized tonic seizures decreased to weekly seizures. The weekly seizures continued and the abnormal EEG including GSSW and GPFA also continued. She underwent CC at 20 years of age, however she has had weekly seizures until age 23, which was the last visit. In this case, KD and VNS were regarded as responsive treatments, while CC was unresponsive. As above, evaluating long term outcomes of each treatment is often complex because patients usually have multi-treatments and multiple seizures during the disease course. Additional factors such as complications, compliance and concomitant AEDs can also affect the outcome.

Previous studies that surveyed outcomes of each treatment were limited to a short-term follow-up duration. Meta-analysis comparing outcomes of VNS vs. CC in LGS concluded that CC is significantly more effective than VNS (80.0% vs. 54.1%, $p<0.05$) in LGS patients with an atonic type of predominant disabling seizure.[22] For all other seizure types, VNS offers comparable rates to CC (49.3% vs. 63.0%).

This study included 17 VNS and 9 CC studies and the mean VNS follow-up duration was 16.23 ± 12.39 months and CC was 37.76 ± 24.05 months. My results indicated that there was a 28.6% response rate in VNS and 29.4% of the CC outcomes were lower than the previous results. This may be associated with

the long-term follow-up period in our study, which included 63.6 ± 30.1 months of VNS and 72.8 ± 47.0 months of CC. The efficacy of KD in LGS was studied at Johns Hopkins hospital and showed a response rate of 44% after 12 months.[23] Meta-analysis that included the largest proportion of eligible patients in our institution (79/189, 41.8%) concluded that 47% of children with LGS had more than a 50% seizure reduction after 3 to 36 months of ketogenic diet treatment.[23,24] The response rate results indicated that 31.6% were also associated with subject characteristics, and all subjects were more than 18 years of age. Patients were followed until adulthood to compare the previous results of short term follow-up, and the overall outcomes of each treatment, which were poorer.

In this study, resective surgery was performed in 18 patients. In previous reports from our institution, 27 patients with LGS with generalized EEG abnormalities received resective surgery, and after 33.1 months of follow-up, 59.3% became seizure-free.[25] However, after long-term follow-up, the outcome was poorer than before, and resective surgery showed better efficacy than any other treatment modalities. Removal of the causative cortical lesion could lead to a fundamental cure, because lesions include cortical development malformations and encephalomalacia after trauma or infection and tumor and tuber.

The pathogenesis of LGS has not been completely understood until now. Successful treatment with resective surgery could explain the causative role of cortex in LGS. The most widely accepted theory is that a certain insult that occurs in the immature nervous system increases cortical excitability and causes bilateral epileptiform discharges.[26] On the contrary, an alternative hypothesis is that the brain reacts to the epileptic process by hypoexcitability as a protective mechanism and hypoexcitability may be a mechanism for the neurobehavioral comorbidities in LGS.[27] A study demonstrated decreased interictal cortical excitability using transcranial magnetic stimulation (TMS).[27] However, the

pathogenesis of LGS cannot be explained by only the cortex. In practice all patients who had resective surgery did not become seizure-free, and some studies have demonstrated that there are thalamus or brain stem abnormalities in LGS. EEG and functional MRI studies revealed that significant activation of the brainstem and thalamus is associated with epileptiform discharges in patients with LGS.[28] An autopsy study in patients with infantile spasms and LGS demonstrated specific morphologic changes in the brainstem.[29] Furthermore, PET studies in children with infantile spasms also revealed hypermetabolism in the brainstem.[30] Successful treatment of LGS with deep brain stimulation in the thalamus also proved the significant role of the thalamus in the pathogenesis of LGS.[31] Both animal studies and clinical studies have demonstrated that the thalamocortical pathway plays an important role in LGS.

This study was limited by the retrospective design, therefore, we were unable to demonstrate the exact process and effectiveness of each treatment modality. However, diverse treatments including KD, VNS, CC or resective surgery can be effective for controlling intractable seizures instead of just AEDs. We retrospectively reviewed the medical records of adult patients with LGS who had been followed up until the time of study. This study may also contain selection bias because patients who were lost because of death, a hospital change or that stopped treatment were not included. All of the patients did not conduct each evaluation at regular intervals which may also limit the information. Despite these limitations, this study is important because it analyzed changes in clinical traits and electrophysiologic features in adult patients with LGS to determine long-term and diverse treatment outcomes.

V. CONCLUSION

In summary, seizures and EEGs changed with age. Although the frequency and intensity of seizures decreased, 76.5% of the patients sustained seizures which were mainly generalized tonic, atonic or generalized tonic-clonic seizures. Characteristic EEG features of DSSW and GPFA disappeared in half of the patients. In regards to cognitive function, 94.7% of the patients had moderate to profound mental retardation independent of many clinical factors or seizure outcomes. Only 39.7% of the patients had the possibility of independent daily living skills and 25.4% could not walk even with support. Although LGS is an intractable epileptic condition, it is important to apply diverse treatments, including KD and surgeries, to the patients who have had unsuccessful previous treatments which can allow for successful seizure control.

REFERENCES

1. International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389-99.
2. Arzimanoglou A, French J, Blume WT, Cross JH, Ernst JP, Feucht M, et al. Lennox-Gastaut syndrome: A consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurol 2009;8:82-93.
3. Trevatham E, Murphy CC, Yeargin-Allsopp M. Prevalence and Descriptive Epidemiology of Lennox-Gastaut syndrome among Atlanta Children. Epilepsia 1997;38:1283-8.
4. Roger J, Remy C, Bureau M, Oller-Daurella L, Beaumanoir A, Favel P, et al. Lennox–-Gastaut syndrome in the adult. Revue Neurologique 1987; 143:401–5.
5. Ohtsuka Y, Amano R, Mizukawa M, Ohtahara S. Long-term prognosis of the Lennox–-Gastaut syndrome. Jpn J Psychiatr Neurol 1990; 44:257–64.
6. Oguni H, Hayashi K, Osawa M. Long-term prognosis of Lennox—Gastaut syndrome. Epilepsia 1996;37 Suppl 3:44-7.
7. Engel J Jr. Epilepsy surgery. Curr Opin Neurol 1994;7:140–7.
8. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders.4th ed. American Psychiatric Association, Washington, DC 1994.
9. Yagi K. Evolution of Lennox-Gastaut syndrome: a long-term longitudinal study. Epilepsia 1996;37 Suppl 3:48-51.d
10. Ferlazzo E, Nikanorova M, Italiano D, Bureau M, Dravet C, Calarese T, et al. Lennox-Gastaut syndrome in adulthood: clinical and EEG features. *Epilepsy Research* 2010;89:271–7.

11. Kotagal P. Multifocal independent spike syndrome: relationship to hypsarrhythmia and the slow spike-wave (Lennox-Gastaut) syndrome. Clin Electroencephalogr 1995;26:23-9.
12. Goldsmith IL, Zupanc ML, Buchhalter JR. Long-term seizure outcome in 74 patients with Lennox-Gastaut syndrome: Effects of incorporating MRI head imaging in defining the cryptogenic subgroup. Epilepsia 2000;41:395-9.
13. Hoffmann-Riem M, Diener W, Benninger C, Rating D, Unnebrink K, Stephani U, et al. Nonconvulsive status epilepticus – a possible cause of mental retardation in patients with Lennox-Gastaut Syndrome. Neuropediatrics 2000;31:169–74.
14. Ogawa K, Kanemoto K, Ishii Y, Koyama M, Shirasaka Y, Kawasaki J, et al. Long-term follow-up study of Lennox-Gastaut syndrome in patients with severe motor and intellectual disabilities: with special reference to the problem of dysphagia. Seizure 2001; 10: 197-202.
15. Perucca E, Gram L, Avanzini G, Dulac O. Antiepileptic drugs as a cause of worsening seizures. Epilepsia 1998; 39: 5-17.
16. VanStraten AF, Ng YT. Update on the management of Lennox-Gastaut syndrome. Pediatr Neurol. 2012;47:153-61.
17. The Felbamate Study Group in Lennox-Gastaut Syndrome. Efficacy of felbamate in childhood epileptic encephalopathy (Lennox-Gastaut syndrome). N Engl J Med 1993;328:29–33.
18. Motte J, Trevathan E, Arvidsson JFV, Barrera MN, Mullens EL, Manasco P; the Lamictal Lennox-Gastaut Study Group. Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome. N Engl J Med1997; 337:1807–12.
19. Sachdeo RC, Glauser TA, Ritter F, Reife R, Lim P, Pledger G; the Topiramate YL Study Group. (1999) A double-blind, randomized trial

of topiramate in Lennox-Gastaut syndrome. Neurology 1999;52:1882–7.

20. Glauser T, Kluger G, Sachdeo R, Krauss G, Perdomo C, Arroyo S. Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. Neurology 2008;70:1950–8.
21. Ng YT, Conry JA, Drummond R, Stolle J, Weinberg MA. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. Neurology 2011;77:1473-81.
22. Lancman G, Virk M, Shao H, Mazumdar M, Greenfield JP, Weinstein S, et al. Vagus nerve stimulation vs. corpus callosotomy in the treatment of Lennox-Gastaut syndrome: a meta-analysis. Seizure 2013;22:3-8.
23. Lemmon ME, Terao NN, Ng YT, Reisig W, Rubenstein JE, Kossoff EH. Efficacy of the ketogenic diet in Lennox-Gastaut syndrome: a retrospective review of one institution's experience and summary of the literature. Dev Med Child Neurol. 2012 May;54(5):464-8.
24. Kang HC, Kim YJ, Kim DW, Kim HD. Efficacy and safety of the ketogenic diet for intractable childhood epilepsy: Korean multicentric experience. Epilepsia 2005;46: 272–9.
25. Lee YJ, Kang HC, Lee JS, Kim SH, Kim DS, Shim KW, et al. Resective pediatric epilepsy surgery in Lennox-Gastaut syndrome. *Pediatrics* 2010;125:58–66.
26. Blume WT. Pathogenesis of Lennox–Gastaut syndrome: considerations and hypotheses. Epileptic Disord 2001;3:183–96.
27. Badawy RA, Macdonell RA, Vogrin SJ, Lai A, Cook MJ. Cortical excitability decreases in Lennox-Gastaut syndrome. Epilepsia 2012;53:1546-53.
28. Siniatchkin M, Coropceanu D, Moeller F, Boor R, Stephani U. EEG-fMRI reveals activation of brainstem and thalamus in patients with Lennox-Gastaut syndrome. Epilepsia 2011;52:766-74.

29. Hayashi M. Neuropathology of the limbic system and brainstem in West syndrome. Brain Dev 2001;23:516–22.
30. Chugani HT, Shewmon DA, Sankar R, Chen BC, Phelps ME. Infantile spasms: II. Lenticular nuclei and brain stem activation on positron emission tomography. Ann Neurol 1992;31:212–19.
31. Samadani U, Baltuch GH. Anterior thalamuc nucleus stimulation for epilepsy. Acta Neurochir 2007; Suppl 97:343–6.

ABSTRACT(IN KOREAN)

레녹스 가스토 증후군의 장기적 추적 관찰 결과

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김 효 정

레녹스 가스토 증후군 환자를 장기간 추적 관찰하여 발작 및 뇌파의 변화, 인지 장애, 운동 장애, 시행한 치료 방법과 발작 조절 효과 및 최종 발작의 정도를 조사 하였다. 레녹스 가스토 증후군을 진단받고 세브란스 어린이병원에서 추적 관찰하고 있는 18세 이상 68명의 환자를 대상으로 후향적 연구를 진행하였다. 환자 연령은 18.7세에서 35.8세 (평균 23.0세) 이었으며 추적 관찰 기간은 8.3년에서 32.5년 (평균 23.0년) 이었다. 발작은 나이가 든 환자에서 강도가 약해지고 빈도가 감소하기는 하였으나 76.5%의 환자에서 발작이 지속되었으며 주로 전신 강직 발작, 전신 강직 간대 발작, 무긴장성 발작이 지속되었다. 발작의 발병 연령, 원인, 뇌 자기공명 영상의 이상 여부, 영아 연축의 유무는 발작의 결과에 영향을 주지 않았다. 레녹스 가스토 증후군의 특징적인 뇌파 양상인 전반적 느린 극서파와 전반적 발작적 속파는 각각 환자의 반 수 에서 없어졌다. 인지기능에 있어서는 94.7%의 환자가 중등도, 중도,

최중도 정신지체에 해당하였고 다른 임상적인 요인이나 발작의 조절 정도와는 무관하였다. 전체 환자 중 39.7%에서만 독립적인 기본적인 일상생활이 가능하였고, 전체 환자의 25.4%는 보행이 불가능하였다. 레녹스 가스토 증후군은 난치성 뇌전증이지만 케톤 생성 식이 요법이나 수술 등 다양한 치료 방법을 시행했을 때 난치성의 일부 환자에서는 성공적으로 발작 조절이 가능하였다.

핵심되는 말: 레녹스 가스토 증후군, 장기간 추적 관찰, 발작 조절