Aims and scope
Annals of Child Neurology is an interdisciplinary peer-reviewed biomedical journal publishing articles in the fields of child neurology, pediatric neurosurgery, pediatric neuroradiology, child psychiatry, pediatric neuropsychology, developmental and behavior pediatrics, pediatric neurosience, and developmental neurobiology. The aims of Annals of Child Neurology are to contribute to the advancements in the fields of pediatric neurology through the scientific reviews and interchange of all of pediatric neurology. It aims to reflect the latest clinical, translational, and basic research trends from worldwide valuable achievements. In addition, genome research, epidemiology, public education and clinical practice guidelines in each country are welcomed for publication.

Focusing on the needs of neurologic patients from birth to age 18 years, Annals of Child Neurology covers topics ranging from assessment of new and changing therapies and procedures; diagnosis, evaluation, and management of neurologic, neuropsychiatric, and neurodevelopmental disorders; and pathophysiology of central nervous system diseases.

Area of specific interest include the following: behavioral neurology & neuropsychiatry, clinical neurophysiology, epilepsy, headache medicine, neurocritical care, neurodevelopmental disabilities, neurogenetics, neuroimaging, neuromuscular medicine, neuroimmunology and inflammation, neuro-oncology, sleep medicine, vascular neurology, as well as other diseases affecting the developing nervous system.

Acceptance for publication of submitted manuscript is determined by the editors and peer reviewers, who are experts in their specific fields of pediatric neurology. The journal includes the following sections: original articles, reviews, letters to the editor. The editorial board invites articles from international studies or clinical, translational, and basic research groups. Supplements can be published when they are required.

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Ji Yeon Lee, Bo Lyun Lee
Purpose: Lennox-Gastaut syndrome (LGS) is one of the most severe epileptic encephalopathies and frequently patients with this syndrome respond poorly to antiepileptic drugs. The aim of this study was to evaluate the treatment outcomes of vagus nerve stimulation (VNS) in LGS patients with drug-resistant epilepsy.

Methods: We analyzed the clinical files, collected over 5 years, of children with LGS who received VNS treatment.

Results: Seven children were included in this study (four males, three females; mean age of VNS insertion 12.4±3.5 years). All the patients had generalized tonic seizures and there were various other seizure types including myoclonic seizures, atonic seizures, and atypical absence seizures. Although two patients had normal imaging, five patients had abnormalities on imaging, including pachygyria, cortical dysplasia, kernicterus, and a chromosomal anomaly. Comparing the baseline seizure frequency to the frequency after the VNS surgery, the seizure frequency at the last follow-up showed a decrease of 57.2% (0% to 100%) on average (P=0.028) and one patient achieved seizure free status. Only two children were given additional antiepileptic drugs with the aim of managing their seizures. There was no mortality or complications related to the VNS therapy except one case requiring intensive care unit admission due to pneumonia. Comparing the results before and after VNS surgery, the VNS therapy also had a tendency to have a positive effect on quality of life (P=0.066).

Conclusion: In LGS patients with drug resistant epilepsy who are not candidates for a corpus callosotomy or resective surgery, VNS could be an effective, low-risk adjunct therapy for decreasing seizure frequency.

Keywords: Vagus nerve stimulation; Lennox Gastaut syndrome; Drug resistant epilepsy; Seizures; Quality of life
Introduction

Lennox-Gastaut syndrome (LGS) is one of the most severe epileptic encephalopathies of childhood onset and accounts for approximately 3% to 10% of all childhood epilepsies [1, 2]. The sex ratio of patients with LGS is reported as half and half [3], and there is a classic triad that defines LGS. First, there are specific electroencephalographic (EEG) patterns consisting of bursts of diffuse slow spike-and-wave complexes less than 2.5 cycles per second in awake patients and generalized paroxysmal fast activity of 10 to 20 Hz mainly during non-rapid eye movement sleep [1]. Second, LGS patients have diverse seizure types such as tonic seizures, atypical absence seizures and drop attacks including head drop or whole body drop [2]. The third feature of LGS is impaired mental function with or without behavioral problems [3].

LGS is regarded as one of the most challenging epilepsies to manage, due to a range of different seizure types which are mostly refractory to antiepileptic drugs (AEDs) [4]. The treatments for LGS can be classified into medication, diet and surgery. The AEDs such as valproic acid, clonazepam, topiramate, levetiracetam, lamotrigine and rufinamide are considered the preferred AEDs, but choosing the most effective AED is challenging and sometimes, based on patient response, a combination of drugs is necessary [3]. Recently, non-pharmacological treatment options have been administered to LGS patients including ketogenic diets, vagus nerve stimulation (VNS), corpus callosotomy and resective surgery. However, most patients with LGS cannot undergo resective surgery due to the multifocal characters of LGS or the difficulty in localizing a single seizure focus [5]. VNS is increasingly being utilized as an adjunctive therapy for patients with drug-resistant epilepsy who are not suitable for resective surgery [6]. The objective of our study was to examine the efficacy of VNS in LGS patients with drug-resistant epilepsy from a single center in South Korea.

Materials and Methods

1. Study population and data source

Between January 2012 and May 2019, a total of 45 patients who met all the criteria of LGS visited the Department of Pediatrics at Chungnam National University Hospital [2, 3]. Among them, seven of these patients (15.6%; four males, three females) who had drug-resistant epilepsy were treated with VNS (Table 1). The first eligibility criterion for the study population was that the age at which the VNS device was implanted was younger than 18 years. The second criterion was that medical records had to contain a minimum of 3 months of data on the patient’s seizure types, frequency, and severity prior to implantation and a minimum of 24 months of follow-up data following implantation.

In addition to demographic characteristics of the patients, some features, such as the patient age at the initial visit and during the follow-up period, were obtained retrospectively from the medical records. The clinical data were also collected retrospectively from the medical records and included the age at seizure onset, age at implant, latent period until surgery, post operation follow-up period, previous history of infantile spasms and diet therapy, seizure types, cognition, and etiology.

The study focused on assessing the change in seizure frequency of the predominant seizure type from baseline, meaning the 3-month period prior to implantation, to 24 months following implantation. The predominant seizure type was defined as the most disabling seizure type noted in the medical records, not necessarily the most frequent seizure type. This study utilized a six-point seizure frequency scale [7], and a therapy responder was classified as a ≥ 50% reduction in baseline seizure frequency of the predominant seizure type following surgery. A six-point sei-

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Table 1. Patients demographical and clinical profiles

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male/female</td>
<td>4 (57.1):3 (42.9)</td>
</tr>
<tr>
<td>Age at seizure onset (yr)</td>
<td>3.5 ± 4.0 (0.0–12.0)</td>
</tr>
<tr>
<td>&lt;1</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td>3–6</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td>&gt;6</td>
<td>1 (14.2)</td>
</tr>
<tr>
<td>Age at surgery (yr)</td>
<td>12.4 ± 3.5 (5.3–16.5)</td>
</tr>
<tr>
<td>&lt;6</td>
<td>1 (14.2)</td>
</tr>
<tr>
<td>&gt;10–16</td>
<td>5 (71.6)</td>
</tr>
<tr>
<td>&gt;16</td>
<td>1 (14.2)</td>
</tr>
<tr>
<td>Latent period of surgery (yr)</td>
<td>9.0 ± 5.2 (1.7–14.9)</td>
</tr>
<tr>
<td>Postoperation follow-up period (mo)</td>
<td>38.8 ± 6.4 (29.7–49.7)</td>
</tr>
<tr>
<td>Seizure types</td>
<td></td>
</tr>
<tr>
<td>Generalized tonic</td>
<td>7 (100.0)</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td>Atonic</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Atypical absence</td>
<td>1 (14.2)</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td>Pachygyria</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>Diffuse cortical dysplasia</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Kernicterus</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Chromosome abnormality</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td>Previous history of infantile spasms</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>Previous history of diet therapy</td>
<td>3 (42.9)</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± standard deviation (range).
ure frequency scale recorded the clinician’s assessment of the patient seizures as "seizures increased," "≤ 24% seizure reduction or no change in seizure frequency," "25% to 49% seizure reduction," "≥ 50% to 90% seizure reduction," "no seizures reported," and "unknown." The safety of VNS was monitored by assessing the incidence of all adverse events (AEs) starting from the day of implantation. Clinicians’ assessments of health outcomes were made using the Clinical Global Impression of Improvement (CGI-I) rating scale.

2. VNS insertion and parameters
VNS (VNS pulse® 102-103, Cyberonics Inc., Houston, TX, USA) insertion was performed by otolaryngologists under general anesthesia and took approximately 2 hours and was done following standard surgical procedure [8]. The procedure includes attaching electrodes to the vagus nerve in the left cervical region, connecting the bipolar lead of the electrodes to a small generator and implanting it under the skin of the left chest region. After a recovery period, the stimulation values were programmed during the outpatient visit. For all the patients, the stimulation frequency was set as 30 Hz with a pulse width of 500 µs. However, a few parameters were adjusted in each patient once the possibility of complications or changes in the seizure frequency were factored in. The stimulation strength was set to 1.5 mA for one patient, 2.0 mA for five patients, and 2.25 mA for one patient. The non-stimulating time after 30 seconds of stimulation was adjusted as 3 minutes for three patients and 5 minutes for four patients, and this pattern was programmed to repeat every 24 hours.

3. Statistical analysis
The statistical analysis was done by SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). The Wilcoxon Rank Sum test was applied to the data to compare non-parametric variables and a P-value of < 0.05 was regarded as statistically significant.

4. Ethics
This study protocol was reviewed and approved by the Institutional Review Board of Chungnam National University Hospital (2017-01-041). Due to its retrospective nature, the study was exempted from requiring informed consent from the participants.

Results

1. Demographic and clinical characteristics of the study patients
A total of seven patients (four males, three females) with a VNS therapy device implanted were included in this study. The average patient age at seizure onset was 3.5 ± 4.0 years (range, 0.0 to 12.0). Fig. 1 shows that three patients were younger than 1 year, three patients were 3 to 6 years and only one patient was older than 6 years. The average age at surgery was 12.4 ± 3.5 years (range, 5.3 to 16.5), one patient was younger than 1 year, five patients were 10 to 16 years and the other one patient was older than 16 years. Period until surgery was 9.0 ± 5.2 years (range, 1.7 to 14.9) and the postoperative follow-up period was 38.8 ± 6.4 months (range, 29.7 to 49.7).

In our study patients had more than one seizure type, so there are a number of findings that overlap in Table 2. All the patients had generalized tonic seizures and there were five with myoclonic seizures, four with atonic seizures, and one with atypical absence seizures. Three patients had normal imaging, while four pa-

![Fig. 1. Seizure frequency before vagus nerve stimulation operation (OP), at 6, 12, 18, 24, 30, 36, 42, and 48 months after the operation. The frequency was reported by caregivers at the outpatient pediatrics clinic of Chungnam National University Hospital. PT, patient.](https://doi.org/10.26815/acn.2019.00108)
tients showed abnormal image findings relating to etiology, including two with pachygyria, one with diffuse cortical dysplasia, and one with kernicterus. One patient had a chromosomal abnormality. Furthermore, there were two patients with a previous history of infantile spasms and three patients with a previous treatment history of diet therapy.

2. Clinical outcomes after VNS insertion

Table 3 shows that the mean follow-up period after VNS insertion was 38.8 months (range, 29.7 to 49.7). When compared with the baseline seizure frequency, the frequency at the last follow-up decreased by 57.2% on average. The largest reduction was 100.0% (from 50 to 0 times per month) and the smallest was 50.0% seen in two patients (from 240 to 120 and from 120 to 60 times per month), with the latter nonetheless a responder. The patient with the largest reduction of seizure frequency was seizure free during the last 12 months of follow-up. In contrast, there was one patient with a 6.7% increase in seizure frequency (from 15 to 16 times per month). The baseline and change in seizure frequency of each patient at 6-month intervals and at the last follow-up are shown in Fig. 1. Using the seizure frequency before surgery and at the last follow-up, the P-value was 0.028 which it is statistically significant. Looking closer, there were some fluctuations in seizure frequency during the follow-up period, but all the patients showed a ≥ 50% reduction in seizure frequency from the first postoperative visit, classifying them all as responders.

As can be seen in Tables 3 and 4, most patients took the same number of AEDs from baseline until last the follow-up visit. The exceptions were two children, where AEDs were added (from 3 to 4 and from 3 to 5) and one child who's AEDs were reduced (from 7 to 4). The number of AEDs were adjusted at outpatient follow-up visits based on the symptoms and overall condition of the patient. All the children with increase number of AED keep the existing drugs and started to take clobazam, and lacosamide plus vigabatrin each. Both of them got the decreased seizure frequency for at least 6 months after VNS surgery without any changes on

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Severity of illness Before</th>
<th>Severity of illness After</th>
<th>CGI-I</th>
<th>Efficacy index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>7</td>
<td>4</td>
<td>Unchanged</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>Minimal</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>Marked</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>Minimal</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>Minimal</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>Minimal</td>
</tr>
</tbody>
</table>

Description of the grades

0 = Not assessed
1 = Normal, not at all ill
2 = Borderline mentally ill
3 = Mildly ill
4 = Moderately ill
5 = Markedly ill
6 = Severely ill
7 = Among the most extremely ill patients

CGI-I, Clinical Global Impression of Improvement.

Table 4. Retrospective studies on vagus nerve stimulation efficacy South Korea

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>No. of centers</th>
<th>Total no.</th>
<th>Patients with VNS</th>
<th>Patients with LGS</th>
<th>Follow-up period</th>
<th>Patients with greater than 50% reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>You et al. (2005) [21]</td>
<td>Intractable pediatric epilepsy</td>
<td>Single</td>
<td>7</td>
<td>7</td>
<td>2</td>
<td>12–44 mo</td>
<td>71</td>
</tr>
<tr>
<td>Kang et al. (2009) [22]</td>
<td>Intractable pediatric epilepsy</td>
<td>Single</td>
<td>297</td>
<td>5</td>
<td>2</td>
<td>6–88 mo</td>
<td>40</td>
</tr>
<tr>
<td>Yum et al. (2007) [23]</td>
<td>Lennox-Gastaut syndrome</td>
<td>Single</td>
<td>79</td>
<td>7</td>
<td>7</td>
<td>5.0 ± 3.3 yr</td>
<td>29</td>
</tr>
<tr>
<td>Current study</td>
<td>Lennox-Gastaut syndrome</td>
<td>Single</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>3.2 ± 0.5 yr</td>
<td>86</td>
</tr>
</tbody>
</table>

VNS, vagus nerve stimulation; LGS, Lennox-Gastaut syndrome.
the existing AEDs. A few months after VNS operation, the number of AEDs were adjusted at outpatient follow-up visits based on the symptoms and overall condition of the patient. Even with the adjustment of AEDs, there was no difference in seizure frequency of two children over 1 year after adding new drugs.

In terms of complications, one patient was admitted to the intensive care unit (ICU) because of pneumonia that developed on day 4 postsurgery which was further complicated by atelectasis and a right-sided pleural effusion. The patient stayed in ICU for 17 days receiving the necessary treatment for the pneumonia and was discharged from the hospital in good condition on day 30 postsurgery. Apart from this patient, there were no other AEs relating to the surgery, including the more common neurological complications such as a hoarse voice.

3. Level of benefit achieved with adjunctive VNS therapy over time
The level of benefit, relating to quality of life (QOL), gained from adjunctive VNS therapy was assessed by the physician following at least 24 months of VNS treatment. Table 4 shows the assessment of the patient’s overall condition and makes a comparison of the patient’s condition before and after VNS insertion. Three children experienced no change and four patients had an improvement in illness severity. Among those that saw an improvement, two children’s assessments went from “markedly ill” to “moderately ill,” and the most improved patient was assessed as “borderline mentally ill” where it was previously “severely ill.” The remaining patient was initially assessed as “among the most extremely ill patients” (the worst possible condition before VNS insertion) and even her condition improved, assessed as “markedly ill” postoperatively, which is a two-step improvement ($P = 0.066$).

As can be seen in Table 4, when using the GCI-I scale, “very much improved” was the best result occurring in patient 4. Patient 2 placed second with a result of “much improved,” followed by the “minimally improved” result seen in patients 3, 5, 6, 7 and finally a result of “no change” in patient 1. Patient 1 also obtained the result of “unchanged” on the efficacy index, while four patients scored “minimal,” one “moderate,” and one “marked.”

Discussion
LGS is a severe childhood-onset epileptic syndrome characterized by multiple seizure types with high frequency, mental retardation and an EEG pattern of diffuse, slow spike-wave complexes and generalized fast activity. In most cases LGS responds poorly to AEDs [5]. Previous studies have reported that only 6.7% to 13.7% of patients achieve seizure freedom with pharmacotherapy [9]. Various treatment options have recently been applied in LGS patients, including ketogenic diets, resective surgery, corpus callosumy and VNS. However, the majority of LGS patients are not candidates for resective surgery due to the multifocal characteristics of the disease or the difficulty to localize a single seizure focus [10]. When medication fails and resective surgery is impossible, other alternative therapies are considered [8].

VNS can be offered as one of these alternative therapies. It is a type of palliative surgery that was originally approved by the Food and Drug Administration in 1997 as an adjunctive therapy for adults and adolescents who are not eligible for resective surgery [5]. VNS is one of the most common neuromodulation-based therapies available. The VNS system consists of a battery-powered pulse generator implanted below the clavicle and a lead that is wrapped around the left vagus nerve in the carotid sheath [11]. Although complete seizure freedom with VNS insertion is rare, it is often beneficial in reducing seizure frequency and improving QOL [12].

Recently, many studies have reported that VNS therapy might be helpful to decrease seizure frequency. Gonzalez et al. [11] examined several studies assessing VNS efficacy and summarized that blinded randomized controlled trials for both children and adults with intractable epilepsy demonstrated that 23% to 57% of patients attain responder status (a seizure frequency reduction of at least 50%) with short-term follow-up. In a multicenter study, De-Giorgio et al. [13] provided further evidence of VNS efficacy with the publication of a non-blinded randomized controlled trial of VNS implantation in 28 participants, resulting in a median seizure reduction of 30% and 45% of patients achieving responder status. From a systematic literature review Gonzalez et al. [11] also suggested that long-term studies have shown a progressive increase in response to VNS as duration of implantation increases. The data they examined, from 2,869 patients across 78 studies, showed an increase in both responder rate and seizure freedom rate over time [11]. Additionally, Kim and Kim [2] treated nine Korean LGS patients with VNS therapy and reported a mean reduction in seizure frequency of 52% after 6 months and 58% after 1 year.

Our study aimed to add further evidence of VNS efficacy in Korean patients, especially after a relatively long period of more than 24 months. Seizure frequency at the last follow-up decreased by 57.2% on average compared with the baseline and with non-parametric statistics a $P$-value of 0.028 was produced, which means that VNS resulted in a statistically significant decrease in seizure frequency. Examining the changes in seizure frequency in further detail, all the patients were responders directly after the VNS surgery. After several unstable months with significant fluctuations, the seizure frequency of most patients settled at a specific level and was subsequently maintained.

https://doi.org/10.26815/acn.2019.00108
At the last follow-up visit one patient was completely seizure free, but one patient was reported as having a similar seizure frequency compared to the baseline. The first child stopped having seizures 18 months after the VNS surgery and remained seizure free for 12 months. According to Braakman et al. [4], seizure freedom in LGS may rarely be achieved by VNS therapy and has been reported after a period of three years of VNS, which means our patient had a rapid response. In the study of Gonzalez et al. [11] 60% of patients achieved responder status following VNS and only 8% of patients were seizure-free at the last follow-up. Therefore, it is necessary to monitor the patient’s seizure frequency regularly for few more years, even if the child does not have any seizures, before making an accurate judgement about seizure-free status.

The second child with the similar seizure frequency compared to the baseline was a responder initially, directly after the VNS operation. The child’s baseline seizure frequency was 15 which is relatively low and there were continuous fluctuations in seizure frequency after the VNS surgery. Just 6 months before his last follow-up visit the patient was a responder. With the initial baseline seizure frequency low, one can argue that smaller changes in frequency may be more significant for this patient than in a patient with a high baseline frequency. Thus, it might not always be that important to assess the exact reduction in monthly seizures, but rather evaluate the patient’s overall condition and subjective benefit, while monitoring changes in seizure frequency at regular intervals on a long-term basis.

VNS therapy has been reported to have a positive influence on QOL by several articles [14,15]. Clark et al. [16] suggested that the QOL in patients with over 50% seizure reduction after VNS surgery were mainly due to the improvement of alertness, memory, and emotion. In our study clinician’s utilized the CGI-I scale to assess the patient’s overall condition while the severity of illness and efficacy index scales were used to examine the outcomes of the VNS therapy. At the last follow-up assessment, there were four patients that scored “minimally improved,” one patient “much improved,” one patient “very much improved,” and one patient “no change.” A non-parametric test produced a P-value of 0.066 and as it is greater than 0.05 it means that there is no statistically significant improvement with VNS on the CGI-I scale. However, the P-value was close to 0.05, so it appears that VNS tends to produce a positive effect on the CGI-I scale.

Several studies on the effects of VNS have also reported improvements of other factors related to QOL, including alertness, concentration, energy, memory, mood, verbal communication, progress with schoolwork and development of life skills [7]. Zamponi et al. [17] found that one-third of patients improve their adaptive behavior and half of patients reported a better QOL, despite epilepsy severity. Orosz et al. [7] showed an improvement in alertness in 66.1% of patients with adjunctive VNS and benefits in the areas of concentration, energy, mood, verbal communication and progress with school work in about one-third of patients at 24 months follow-up. Our study also gathered data relating to QOL from patients and caregivers at the outpatient visits. All the patients experienced improvement in alertness and there was one patient with a gradual reduction in drooling. Furthermore, one patient became potty-trained after VNS surgery which positively affect not only the quality of the patient’s life, but also that of the caregiver’s. One caregiver of another patient also expressed satisfaction about VNS therapy, reporting that the patient who was in a wheelchair at the first visit of the clinic became to be able to walk alone and have better communication skills with improvement of alertness. As mentioned like this, there were subjective descriptions from caregivers representing diverse range of symptom relieves and better conditions of the LGS patients. The current study did not set specific parameters relating to QOL, but by providing the caregiver or patient with a survey that includes common elements of QOL, such as alertness, global interaction, or night-time sleep, more objective and accurate data can be obtained, particularly over a longer time period.

By anchoring and stimulating the vagus nerve, the VNS system lets patients control over-excitabilities without damaging brain tissue, and depending on the symptoms, modulate stimulation intensity [2]. Despite these advantages, there are complications of VNS therapy which can be classified into two categories: (1) those associated with surgical implantation and (2) those related to electrical stimulation [18]. According to Giordano et al. [19], the complications related to surgery include intraoperative bradycardia and asystole during lead impedance testing, hematoma, infections, and vagus nerve injury resulting in hoarseness, dysphagia due to left vocal cord paralysis. However, in most cases the paralysis only persists for a few months and then resolves [19]. As mentioned, patients can also suffer from complications associated with electrical stimulation of the vagus nerve. Examining several studies on the complications of stimulation, Gonzalez et al. [11] concluded that hoarseness is the most prevalent adverse effect and some studies have recently suggested an association between VNS and sleep apnea. In our study, there was only one patient who was admitted to the ICU due to pneumonia which, as an infection following the operation, can be classified as a complication of the VNS surgery. Apart from this case, there were no other complications related to the VNS surgeries and no symptoms associated with stimulation such as hoarseness, stimulation of the phrenic nerve due to proximity or obstructive sleep apnea.

There were four retrospective studies on VNS efficacy pub-
lished in South Korea. Thus, the present article briefly reviewed those studies with Table 4 and looked into similarity or difference comparing to the current study. Kim et al. [20] retrospectively reviewed medical records of 12 patients (nine of them were LGS patients) with intractable children epilepsy who got VNS insertion from two university hospitals, and 67% of the whole patients got over 50% reduction of seizure frequency. Among those patients, one patient with partial seizure showed a 90% reduction, and another patient originating from previous encephalitis got a 75% reduction at 12 and 24 months. Also, there were two patients with some improvements on EEG. Hoarseness, respiratory difficulty during sleep, infection of the surgical wound, increased salivation, and failure of pulse generator were transiently presented as the complications of VNS, and relieved after coordinating output current of the generator. You et al. [21] also retrospectively reviewed medical records of seven patients (two of them were LGS patients) with intractable children epilepsy who got VNS insertion from one medical center, and 71% of the whole patients showed greater than 50% reduction of seizure frequency. They indicated that the seizure reduction appeared 3 months after VNS insertion, and mentioned positive effects on EEG and QOL. The study also reported VNS complications such as hoarseness and wound infection appeared in few cases for short period.

Kang et al. [22] also retrospectively studied medical records on 297 patients with intractable children epilepsy, which is relatively big number compared with other studies from single medical center. They investigated the effects of antiepileptic drugs, prednisolone, ketogenic diet, epilepsy surgery, and VNS. Among the whole study population, five patients got VNS insertion and two of them were diagnosed with LGS. Over 50% reduction of seizure frequency was appeared at 40% of those five patients, and the study concluded that VNS therapy appears to be successful regardless of seizure type or cause and attractive as non-pharmacologic aspects. Lastly, Yum et al. [23] retrospectively checked medical records on 79 LGS patients at one medical center and there were seven patients who got VNS therapy among the whole study population. Greater than 50% reduction of seizure frequency were shown at 29% among those seven patients. Due to errors of pulse generator, one patient appears to have severe symptoms of stimulated vagus nerve, but continue the state of seizure free for several weeks at the same time. The study claimed that the number of patients with VNS therapy was too small to clearly figure out the efficacy of VNS, but there was no critical complication.

Although there were some differences between those four studies and the present study, the conclusion that VNS appears to be effective and safe choice for VNS was common. Also, the four studies and the current study similarly examined the efficacy of VNS with seizure frequency reduction and mentioned complications of VNS therapy. Unlike the four articles which had relatively short minimum follow-up period or checked the seizure frequency for every 12 months, the present article indicated seizure frequency of each patient more specifically on Fig. 1, for every 6 months during relatively long follow-up period with minimum of 24 months. Looking through the Fig. 1, readers would be able to see the overall flow of seizure frequency on each patient. Also, You and colleagues mentioned the effects of VNS on QOL of the patients only with the reports from caregiver about few factors related to QOL such as alertness, communication or exercise skills. On the other hand, the present article described QOL with both CGI-I scale and reports from caregivers of the patients, differed from the other studies.

The present study has a few potential limitations. The study was based on the data of only seven patients at a single medical center. It would be of great help to recruit additional patients by cooperating with other hospitals to draw more universal conclusions and identify various etiologies. Although all the follow-up periods of seven patients was more than 24 months, performing consistent follow-up for each patient would also enable the collection of broader data. The other limitation is that our study mainly utilized caregivers’ reports to assess changes in seizure frequency. Considering the age of the patients and specificity of current equipment available used to monitor for seizures such as generalized tonic-clonic seizures, using a device like an epilepsy-recording bracelet might be helpful to gather more objective and accurate data.

Our study established that VNS therapy positively affects LGS patients in terms of decreasing seizure frequency and improving QOL. Apart from rare complications from the VNS surgery and vagal stimulation, VNS can be regarded as a relatively safe and effective treatment modality for patients with LGS, which is a very challenging epileptic encephalopathy to manage. In future, more multicenter studies with more objective data collection conducted over longer time periods are necessary for further evidence of VNS use in LGS. As mentioned before, most studies about VNS including the current study examine the medical records retrospectively. For establishing VNS as a safe and reliable option to pharmaco-resistant epileptic patients, it would be helpful to follow-up on patients who received VNS therapy decades ago in their childhood, and prospectively identify the current efficacy plus any late complications.

Conflicts of interest

No potential conflicts of interest relevant to this article were reported.
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References

18. George MS, Aston-Jones G. Noninvasive techniques for probing neurocircuitry and treating illness: vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Neuropsychopharmacology 2010;35:301-16.
Purpose: Childhood absence epilepsy (CAE) is a common form of idiopathic generalized epilepsy with onset middle childhood and has typically a good prognosis, but remission rates vary. We aimed to analyze unfavorable prognostic factors in children initially diagnosed with CAE.

Methods: We retrospectively reviewed 48 patients under 13 years of age who were diagnosed with CAE at the Severance Children's Hospital, Seoul, Korea. We analyzed clinical information including comorbidity through neuropsychological test.

Results: Thirteen of the 48 patients (27%) showed an unfavorable prognosis, with clinical seizures or seizure waves on electroencephalogram persistent even after 12 months of anticonvulsant therapy. The mean age at absence seizure onset was 6.51 ± 2.36 years. The most commonly used antiepileptic drug (AED) was ethosuximide, and the median duration of initial AEDs was 25.63 ± 24.41 months. The presence of comorbidity and clinical absence seizures after 6 months of AEDs correlated with an unfavorable prognosis. Motor seizures were the most unfavorable prognostic factor during follow-up.

Conclusion: This study shows that clinical absence seizures after 6 months of AED, comorbidity, and motor seizure are the most important predictive factors of an unfavorable prognosis for absence epilepsy in childhood. This study suggests that when these factors are observed, early intervention needs to be considered.

Keywords: Epilepsy, absence; Comorbidity; Prognosis

Introduction

Childhood absence epilepsy (CAE) is a common form of idiopathic generalized epilepsy with onset in middle childhood [1-3]. The definition of CAE is based on the frequency of absences or patterns of recurrence, and on age of seizure onset [4]. The onset age of CAE is usually between 4 and 10 years, and it is characterized by frequent and brief typical absences with abrupt impairments of consciousness. Typically, CAE leads to ictal discharges of generalized high-amplitude spikes and slow complexes on electroencephalogram (EEG) recordings, rhythmic at 3 Hz with normal or mildly abnormal background activity [4-6]. Occipital intermittent rhythmic delta activity (OIRDA) on EEG is seen in one-third of children with CAE. Occasionally, children with absence epilepsy also suffer motor seizures [4]. In most patients, seizures are provoked by hyperventilation [6].

CAE is typically pharmaco-responsive, and usually treated with antiepileptic drugs (AEDs) such as ethosuximide (ETX), valproic acid (VPA), or lamotrigine (LTG) [1,2,7-9]. As the prognosis is related to various aspects of remission rates [2,3,7-9]. Here, we sta-
tistically studied the prognostic factors for absence epilepsy in childhood.

**Materials and Methods**

1. **Patient information**

Patients who were diagnosed and treated with typical CAE at the first onset at the Severance Children’s Hospital, Seoul, Korea between June 2009 and June 2017 were retrospectively reviewed. Typical CAE was defined as patients with pyknolepetic absence seizure and 3 to 4 Hz rhythmic generalized spike-and-wave (GSW) on EEG with normal development. Of the 78 newly diagnosed patients, 48 patients, underwent follow-up EEG at 6 and 12 months, and had started their first AEDs treatment at our hospital, were included. Patients initially diagnosed with CAE were involved in this study, but a percentage of the patients progressed to juvenile myoclonic epilepsy (JME) or juvenile absence epilepsy (JAE).

We analyzed clinical information including sex, age at absence seizure onset, EEG patterns, type and duration of AEDs, hyperventilation provocation test, whether motor seizures occurred during follow-up, and comorbidities. We also evaluated the effectiveness of AEDs at 6 and 12 months, and reviewed EEG pattern at 6 and 12 months under AEDs treatment. In this study, comorbidities analyzed through neuropsychological test including Korean Wechsler Intelligence Scale for Children-III and Korean Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale. We defined a favorable prognosis as no clinical seizures and no seizure waves on EEG after the 12 months of AEDs. We defined an unfavorable prognosis as the presence of clinical or EEG seizures even 12 months after the onset of AEDs.

This study was approved by the Institutional Review Board of Severance Hospital (4-2016-0080). Informed consent was waived due to the retrospective nature of the study.

2. **Statistical analysis**

Data processing and analysis were performed with SPSS version 23.0 (IBM Co., Armonk, NY, USA). We used independent-sample t-tests, Fisher’s exact test, and Pearson’s chi-square test to compare variables and their relationships with prognosis. Multivariate logistic regression models with forward stepwise conditional selection of variables were used to confirm the correlation between each factor and a poor prognosis. A *P* value < 0.05 were considered significant.

**Results**

Table 1 summarizes the main characteristics of two groups, favorable and unfavorable prognosis. The favorable prognosis was defined as no clinical seizures and no seizure waves on EEG after the 12 months of AEDs. The unfavorable prognosis was defined as persistence of clinical seizures or seizure waves on EEG even after the 12 months of AEDs. The Thirteen of the 48 patients (27%), showed an unfavorable prognosis. Twenty-nine patients were female, 19 were male, and the total female ratio was thus 60.4%. Mean age at absence seizure onset was 6.51 ± 2.36 years (range, 3.0 to 12.5), the mean age of the patients with a favorable prognosis was 6.42 ± 2.20 years (range, 3.33 to 12.5), and the mean age of the patients with an unfavorable prognosis were 6.75 ± 2.86 years (range, 3.0 to 1.92), with no significant differences between the groups. In the EEG patterns, 3 to 4 Hz GSW complexes were observed in 35 patients (72.9%) on normal background, and OIRDA was observed in eight patients (16.7%). The median duration of initial AED was 25.63 ± 24.41, 23.63 ± 13.83 months in the group with a good prognosis and 31.00 ± 41.83 months in the group with a poor prognosis, respectively. The hyperventilation provocation test was negative in 13 patients (27.1%).

In 19 patients (39.6%), follow-up EEG was normalized after 6 months of AED therapy, while GSW complexes remained visible in 29 patients (60.4%). In 33 patients (68.8%), clinical seizures improved after 6 months of AED therapy, while clinical seizures were still observed in 15 patients (31.2%). Of the 33 patients who had no clinical seizures after 6 months, only 19 patients also showed improved EEG seizures. Ten patients (20.8%) had at least one motor seizure during the follow-up, and 10 patients (20.8%) had comorbidities. Three of these had ADHD according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV diagnostic criteria, while four patients only had attention deficits. One patient had a tic disorder, one patient had claustrophobia, and two patients had febrile motor seizures. Six of the 10 patients with comorbidities had a poor prognosis.

Three AEDs, ETX, VPA, and LTG were used in this study. The most commonly used AED was ETX (7.5 to 25 mg/kg/day), which was taken by 26 patients (54%). VPA (5 to 30 mg/kg/day) was the second most common AED, and LTG (0.2 to 4.5 mg/kg/day) was the third. Thirty-two of patients (66.6%) used a second AED including VPA, ETX, and LTG due to uncontrolled seizures on the first AED or the side effects of the first AED. When ETX was used as the 1st AED, VPA was used as the 2nd AED in 13 patients (75%), and LTG was used as the 2nd AED in four patients (25%). When VPA was used as the 1st AED, ETX was used as the 2nd AED in seven patients (64%), and LTG was used as the 2nd AED in four patients (36%). When LTG was used as the 1st AED, VPA and ETX were selected as the 2nd AED in the same ratio.
Univariate analysis showed that a clinical seizure even after the first 6 months of AED treatment, at least one motor seizure, and comorbidities, correlated with an unfavorable prognosis (Fig. 1A). The most significant unfavorable prognostic factor was a motor seizure at least once. There was a tendency towards an unfavorable prognosis with the age at absence seizure onset increasing (odds ratio [OR], 1.060), which did however not reach significance (P = 0.668). Although not statistically significant, the prognosis was worse when seizures were not induced by a hyperventilation test (OR, 2.109). The prognosis was poor when GSW were still visible on EEG after 6 months of AED therapy (OR, 5.194), which did however not reach significance (P = 0.050). All results are shown in Fig. 1.

The independent variables that were significant in univariate analysis were tested using a multivariate logistic regression analysis with a forward stepwise conditional selection method. Motor seizures ranked first in the factor hierarchy of unfavorable prognosis (OR, 105.825), followed by comorbidities (OR, 14.154) (Fig. 1B). Clinical absence seizures 6 months after AEDs did not reach significance in the multivariate analysis (P = 0.082).

Discussion

The purpose of our study was to statistically analyze prognostic factors in children with absence epilepsy, confirming the prognostic factors identified in previous studies, and determining new predictors. Among the patients diagnosed as CAE initially, the unfavorable prognostic factors were motor seizure, comorbidity, and clinical absence seizure 6 months after the start of AEDs. Because the prognosis may vary according to patient selection, patients were selected according to the International League Against Epilepsy (ILAE) criteria for JAE, JME, and CAE. CAE differs from JAE in that the onset age is lower and absence seizures occur more frequently [1,8]. JAE presents in late childhood or adolescence with less frequent typical absences and generalized tonic-clonic seizures (GTCs). JME usually presents in adolescence with prominent myoclonic jerks that characteristically occur in the morning, and GTCs [8]. The overall prognosis of CAE is favorable but remission rates vary [2,3,7,9]. Previously known favorable prognostic factors include a shorter interval to loss of 3-Hz spike-and-wave complexes, the presence of OIRDA on EEG, and a prompt re-

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sponse to AEDs [2,3]. Unfavorable prognostic factors include late onset age, nonpyknoletic absence seizure patterns, later development of myoclonic attacks or GTCs, atypical EEG features, psychiatric comorbidities, and side effects of AEDs [2-4,6,8,10,11].

In an earlier study, of 39 adult patients with typical absence seizures from 10 years of age, 12% were diagnosed with JAE and 7% with JME [12]. There is however a period of overlap between CAE and JME. In a retrospective study, 18% of patients diagnosed with JME evolved from CAE [13]. Linkage to chromosome 1 has also been reported in patients with absence seizures from childhood that were later diagnosed with JME [6,14]. In addition, several chromosomal loci have been identified in families of patients with absence seizures from childhood [6,15]. Recently, several epilepsy genes have been found in idiopathic generalized epilepsies with unclear family history and a genetic mutation in gamma-aminobutyric acid receptor alpha-1 has been found in CAE and JME [6,16].

In this study, only monotherapy was started at the time of initiation and more than 50% of patients started treatment with ETX, considering the effects and side effects. This study shows that the presence of clinical absence seizures after 6 months of taking AEDs, motor seizures, and comorbidities are the most important predictive factors for an unfavorable prognosis. Generally, GTC or myoclonic jerks are not suitable for CAE diagnosis. However, in this journal, we tried to evaluate whether the prognosis is worse if patients initially diagnosed with typical CAE had even once motor seizure. In patients initially diagnosed with typical CAE, those with motor seizure progressing to JAE, JME showed the most unfavorable prognosis.

In this study, neuropsychological tests were performed at the time of the first diagnosis to check for neurodevelopment status and unknown comorbidity such as ADHD and attention deficits. The prognosis was also unfavorable when there was comorbidity [10,11].

The neuropsychological test follow-up was not performed periodically after diagnosis in this study. But it may be necessary to check psychosocial outcome whether the learning difficulty is affected after diagnosis and treatment by neuropsychological test.

The absence of a clinical seizure within 6 months of taking AEDs can be considered as a good response to treatment. This study is in line with earlier reports showing similar results [2-4,8,10,11]. EEG abnormalities after 6 months of therapy with AEDs was not identified as a poor prognostic factor in this study, as the statistical tests did not reveal significance. However, as in
previous studies, the prognosis was five times worse when GSW complexes were observed on EEG 6 months after the administration of AEDs [2]. An EEG follow-up within 6 months to predict the prognosis would thus seem warranted.

Previous studies have shown a good prognosis with OIRDA and a poor prognosis with EEG polyspikes, but none of these two EEG abnormalities showed a significant correlation with prognosis in this study [2-4,8,10,11]. We assumed that the prognosis would be worse if the duration of visible GSW complexes was long or if they were not easily provoked by hyperventilation, but our analysis did not yield statistical significance.

This study is limited by its retrospective analysis approach as well as by its small sample size and single-center design. In addition, the lack of long-term follow-up observations has limited our assessment of epilepsy syndromes. Further studies are needed to investigate the relationships between prognostic factors and evolution into other epilepsy syndromes, as well as potential relationships with genetic mutations.

In conclusion, our study suggests that in cases of clinical seizures even after 6 months of AED treatment, motor seizures, or comorbidities, early intervention should be considered. A prospective or randomized controlled clinical trial in the future might be able to provide more detailed results.

Conflicts of interest

No potential conflicts of interest relevant to this article was reported.

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References

Efficacy and Tolerability of Low-Dose Perampanel in Patients with Childhood-Onset Intractable Epilepsy

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Purpose: The aim of this study was to evaluate the efficacy and tolerability of perampanel as adjunctive therapy in childhood-onset refractory epilepsy.

Methods: We retrospectively reviewed the medical records of 110 patients who were treated with perampanel in Asan Medical Center children's hospital. Two patients with poor compliance were excluded and 108 patients were enrolled. The clinical characteristics were reviewed, and the total seizure frequency before and after the add-on of perampanel was analyzed.

Results: The mean age of the patients (64 males) was 20.2 years (range, 10.5 to 35.6). The mean maintenance dose was 4.8 mg/day (2 to 10 mg). Eight patients (7.4%) achieved seizure freedom and 35 (32.4%) achieved a seizure reduction of ≥50%. Among them, three patients achieved seizure freedom with only 2 mg/day of perampanel. There was no significant difference in sex, age at seizure onset, duration of epilepsy, use of concomitant enzyme-inducing antiepileptic drugs, number of concomitant antiepileptic drugs, and adverse events between responders and non-responders. The retention rate was up to 68.0% in the first year and 59.5% in the second year of the study. Thirty-four patients (31.5%) reported adverse events: violence, somnolence, dizziness, drooling, weight gain, insomnia, and vomiting. There was no contributing factor for the adverse events, including sex, age, and the number of concomitant antiepileptic drugs and enzyme-inducing antiepileptic drugs when comparing the adverse event present group with the adverse event absent group.

Conclusion: Low-dose perampanel showed reasonable efficacy and tolerability in patients with refractory childhood-onset epilepsy. Further validation with pharmacokinetic studies is needed.

Keywords: Perampanel; Drug resistant epilepsy; Drug-related side effects and adverse reactions; Treatment outcome

Introduction

Childhood-onset epilepsy is a common neurological disease that affects approximately 0.5 to 1 in every 100 children and young people [1]. Despite the many newly developed antiepileptic drugs (AEDs), 20% to 30% of patients do not achieve acceptable seizure control with the current pharmacotherapy. Drug-resistant seizures can cause cognitive impairment, behavioral and mental health problems, and eventual deterioration of their quality of life [2]. Thus, early seizure control with appropriate AEDs is very important for patients with epilepsy.

Perampanel (PER) is a highly selective, non-competitive, orally
active antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors for glutamate, the major excitatory neurotransmitter in the central nervous system [3-5]. The role of AMPA receptors in the generation and spread of epileptic seizures has been demonstrated in many studies [6-10]. Overexpression of AMPA receptors is also observed in the hippocampal and neocortical tissue of patients with epilepsy [11,12]. PER is mainly metabolized in the liver by cytochrome P450 (CYP3A4/6); therefore, enzyme-inducing antiepileptic drugs (EIAEDs), such as carbamazepine (CBZ), oxcarbazepine (OXC), and phenytoin (PHT), can reduce its concentrations up to 50% to 60% [13] and concomitant use of EIAEDs has been reported as a clinical factor for poor response to PER and concomitant use of EIAEDs has been reported as a clinical factor for poor response to PER [14].

PER was initially approved for adjunctive treatment of focal seizures (with or without secondarily generalized seizures) in patients with epilepsy aged ≥12 years [15]. Lately, the U.S. Food and Drug Administration expanded its indication to monotherapy for focal seizures and pediatric patients ≥4 years [16,17]. Several prospective and retrospective studies have examined the efficacy and tolerability of PER as an adjunctive AED for epilepsy. They reported that PER can reduce the seizure frequency by at least 50% in 34% to 57% of patients with intractable epilepsy [2,18-26].

In this study, we aimed to examine the tolerability and efficacy of PER as adjunctive therapy in patients with childhood onset epilepsy. In addition, we attempted to determine the possible factors associated with the response rate and adverse events.

Materials and Methods

We retrospectively reviewed the medical records of 110 patients who were treated with PER as adjunctive therapy in the Asan Medical Center Children’s Hospital between May 2016 and May 2018.

We included patients with drug-resistant epilepsy, which was defined as having uncontrolled seizures even with two or more appropriate AEDs. Two patients with poor compliance were excluded and 108 patients were enrolled. This retrospective study was exempt from informed consent per our institutional policies and approved by the Institutional Review Board of Asan Medical Center (2019-1058).

The baseline characteristics, including age, gender, seizure onset, and concomitant AEDs were documented from the electronic medical records. We evaluated the efficacy of PER by comparing the total seizure frequency during 3 months before and after the add-on of PER. The seizure frequency was divided into five categories: seizure-free, seizure reduction ≥50%, seizure reduction <50%, no change, and aggravated. Patients who achieved seizure freedom and seizure frequency reduction ≥50% were assigned into the responder group, and the others were assigned into the non-responder group.

The clinical profiles of the patients in both groups were compared, including the age, gender, daily PER dose, number of concomitant AEDs, and the concomitant use of EIAEDs. The dose-related efficacy was also evaluated.

Tolerability was accessed through review of the medical records for the occurrence of adverse events after the addition of PER, as well as by retention rate measurement. According to the presence of adverse events, the patients were divided into two groups: adverse event present group and adverse event absent group. The clinical profiles of the patients in both groups were compared, including the age, gender, daily PER dose, and the number of concomitant AEDs. The retention rate was calculated using the Kaplan-Meier analysis. Statistical analysis was performed using Pearson’s chi-square test and Fisher’s exact test for categorical variables. SPSS software version 21.0 (IBM Co., Armonk, NY, USA) was used for descriptive and statistical analysis. A probability value of P<0.05 was considered statistically significant.

Results

1. Demographic and baseline characteristics of patients

A total of 108 patients were included in the analysis. The median follow-up duration after the start of PER was 15 months (range, 3 to 24). The mean age was 20.2 years (range, 10.5 to 35.6) and 64 patients were male. The mean age at the time of the first seizure attack was 8.0±5.8 years (range, 0.0 to 29.2). The mean number of concomitant AEDs was 3.8±1.0 (range, 2 to 7) (Table 1). The mean maintenance dose was 4.8 mg/day (2 to 10 mg). PER was initiated at a dose of 2 mg once daily at bedtime and the dose was gradually increased in increments of 2 mg at intervals of at least 1 week, while monitoring the seizure frequency and adverse events occurrence. The most commonly used AEDs with PER were clobazam (73.6%), topiramate (54.5%), levetiracetam (51.8%), valproate (38.2%), and lamotrigine (38.2%). The number of patients who were taking EIAEDs (OXC, CBZ, or PHT) were 33 (30%), 15 (13.6%), and two (1.8%), respectively.

2. Efficacy

Among the 108 patients, 43 were classified as responders (43/108, 39.8%), including eight (7.4%) who achieved seizure freedom and 35 (32.4%) who achieved ≥50% seizure reduction. Sixty-five patients (60.2%) were classified as non-responders; 17 (15.7%) with less than 50% seizure reduction, 34 (31.5%) with no change, and 14 (13%) with seizure aggravation after the addition of PER (Fig. 1).
There was no significant difference in the sex, age at seizure onset, duration of epilepsy, number of concomitant AEDs, and adverse events between the two groups (Table 2). The maintenance dose of PER was slightly higher in the responders than in the non-responders (5.3 vs. 4.4, respectively; \( P = 0.04 \)). Only nine of 29 patients treated with 2 mg of PER were responders. There were 46 patients who could tolerate PER at a higher dose (6 to 10 mg). Among them, 23 patients (50%) achieved \( \geq 50\% \) seizure reduction. The response rate at each dose of PER was 0% (0/1) at 1 mg; 31.0% (9/29) at 2 mg; 33.3% (10/30) at 4 mg; 50% (1/2) at 5 mg; 44% (11/25) at 6 mg; 100% (2/2) at 7 mg; 46.7% (7/15) at 8 mg; and 75% (3/4) at a dose of 10 mg (Fig. 2A).

Duration of PER treatment was much longer in the responders than in the non-responders 13.5 months vs. 8.7 months, respectively; \( P = 0.03 \). The number of patients who eventually stopped PER was higher in the non-responders than in the responders (30 vs. 4, respectively; \( P < 0.001 \)). Patients taking EIAEDs showed a similar response rate when comparing the overall efficacy (CBZ 15/33, 44%; OXC 6/15, 40%; PHT 1/2 50%).

Five of 10 patients (50.0%) who were started on PER as the

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### Table 1. Demographics and baseline characteristics of the patients (n=108)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>64 (59.3)</td>
</tr>
<tr>
<td>Female</td>
<td>44 (40.7)</td>
</tr>
<tr>
<td><strong>Age at seizure onset (yr)</strong></td>
<td>8.0 ± 5.8 (0.0-29.2)</td>
</tr>
<tr>
<td><strong>Age at the start of PER (yr)</strong></td>
<td>20.2 ± 5.0 (10.5-35.6)</td>
</tr>
<tr>
<td><strong>Duration of seizures before treatment (yr)</strong></td>
<td>12.1 ± 5.5 (1.2-21.0)</td>
</tr>
<tr>
<td><strong>Mean maintenance dose (mg)</strong></td>
<td>4.8 ± 2.3 (2-10)</td>
</tr>
<tr>
<td><strong>AEDs at baseline</strong></td>
<td>3.8 ± 1.0 (2-7)</td>
</tr>
<tr>
<td>2</td>
<td>10 (9.1)</td>
</tr>
<tr>
<td>3</td>
<td>30 (27.3)</td>
</tr>
<tr>
<td>4</td>
<td>43 (39.1)</td>
</tr>
<tr>
<td>5</td>
<td>19 (17.3)</td>
</tr>
<tr>
<td>6</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>7</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean±standard deviation (range). PER, perampanel; AED, antiepileptic drug.

### Table 2. Comparison of clinical factors between responder and non-responder group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Responders (n = 43, 39.8%)</th>
<th>Non-responders (n = 65, 60.2%)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>27 (61.4)</td>
<td>37 (56.9)</td>
<td>0.64</td>
</tr>
<tr>
<td>Age at seizure onset (yr)</td>
<td>9.1 ± 6.5</td>
<td>7.3 ± 5.2</td>
<td>0.12</td>
</tr>
<tr>
<td>Age at the start of PER (yr)</td>
<td>21.0 ± 5.3</td>
<td>19.8 ± 5.0</td>
<td>0.22</td>
</tr>
<tr>
<td>Duration of seizures before treatment (yr)</td>
<td>11.9 ± 5.6</td>
<td>12.4 ± 5.4</td>
<td>0.61</td>
</tr>
<tr>
<td>Duration of PER treatment (mo)</td>
<td>13.5 ± 7.7</td>
<td>8.7 ± 8.1</td>
<td>0.03</td>
</tr>
<tr>
<td>No. of concomitant AEDs</td>
<td>3.8 ± 1.2</td>
<td>3.8 ± 1.0</td>
<td>0.78</td>
</tr>
<tr>
<td>Any EIAEDs</td>
<td>20 (46.5)</td>
<td>27 (41.5)</td>
<td>0.61</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>15 (34.1)</td>
<td>18 (27.7)</td>
<td>0.43</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>5 (11.4)</td>
<td>9 (13.8)</td>
<td>0.74</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>1 (2.3)</td>
<td>1 (1.5)</td>
<td>0.77</td>
</tr>
<tr>
<td>Maintenance dose of PER (mg/day)</td>
<td>5.3 ± 2.4</td>
<td>4.4 ± 2.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Adverse events</td>
<td>12 (27.3)</td>
<td>22 (33.8)</td>
<td>0.47</td>
</tr>
<tr>
<td>No. of patients of PER discontinuation</td>
<td>4 (11.8)</td>
<td>30 (88.2)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean±standard deviation. PER, perampanel; AED, antiepileptic drug; EIAED, enzyme-inducing antiepileptic drug.
third AED were responders (three achieved seizure freedom and two achieved ≥50% seizure reduction). When PER was added as the fourth, fifth, or sixth AED, the response rate was 36.7% (11/30), 41.8% (18/43), and 21% (4/19), respectively.

There were eight patients who achieved seizure freedom. They had various etiologies—structural (n = 3), unknown (n = 4), and Gaucher disease (n = 1)—and seizure types—focal aware non-motor seizure (n = 1), focal impaired awareness motor seizure (n = 4), and generalized motor seizure (n = 3). Four of them had undergone a prior epilepsy surgery or vagus nerve stimulation due to uncontrolled seizures but had no significant improvement in the seizure frequency. The mean maintenance dose was 4.25 mg/day (n = 3, 2 mg; n = 3, 4 mg; and n = 2, 8 mg). Three of these patients maintained seizure freedom at a PER dose of 2 mg.

3. Tolerability

Thirty-four patients (31.2%) reported any adverse events: violence (15/108), somnolence (8/108), dizziness (8/108), drooling (2/108), weight gain (2/108), insomnia (2/108), and vomiting (1/108) (Fig. 3). The mean daily dose of PER in patients who experienced adverse effects was 4 mg/day (n = 3, 2 mg; n = 3, 4 mg; and n = 2, 8 mg). Three of these patients maintained seizure freedom at a PER dose of 2 mg.

Fig. 2. Seizure outcomes and occurrence of adverse events per daily doses of perampanel (PER). (A) The response rates according to daily PER dose are shown as bar graph. Response rate at dose of ≤4 mg was 31.7% while response rate at dose of 5 to 7 mg was 48.7% and 52.6% at dose of ≥8 mg. Patients who could tolerate PER up to a higher dose had a tendency to relatively better seizure outcomes than that of patients who received lower-dose PER. The response rates at each dose are listed [0% [0/1] at 1 mg; 31.0% [9/29] at 2 mg; 33.3% [10/30] at 4 mg; 50% [1/2] at 5 mg; 44% [1/25] at 6 mg; 46.7% [7/15] at 8 mg; 100% [2/2] at 7 mg; and 75% [3/4] at 10 mg PER]. (B) There was no association between the daily dose and adverse events rate. Twenty-three patients of the 34 in the adverse event group experienced an adverse event at only 1 to 4 mg, whereas 11 patients experienced adverse events during the increasing of the PER dose up to 5 to 10 mg (seven adverse events at 5 to 7 mg; four adverse events at dose of ≥8 mg).
or insomnia, 14/34). Among them, four patients showed seizure aggravation and neuropsychiatric adverse events at the same time. Seven patients who showed no improvement in seizure frequency stopped the PER and one patient who achieved seizure freedom stopped the PER maintain the seizure freedom status after discontinuation of PER.

Among 34 patients who experienced any adverse events, 13 patients stopped the PER immediately and nine patients tried to reduce daily PER dose. Despite PER dose reduction, six patients quitted the PER eventually. After withdrawal of the drug, the neuropsychiatric symptoms spontaneously resolved within weeks in all patients.

### Discussion

This single-center, retrospective study supports the efficacy and tolerability of PER when used as an adjuvant treatment in patients with refractory epilepsy. There have been many studies on the efficacy and safety of PER, from randomized placebo-controlled trials to postmarketing observational studies. Singh et al. [23] reported a 50% response rate (≥50% seizure reduction) in children and adults with various epilepsy syndromes with a mean daily dose of PER of 6.5 ± 3.1 mg (mean, 6). In an open-label extension study, Montouris et al. [27] increased the dose of PER to 12 mg/day or up to the maximally tolerated individual dose. They reported a 55% response rate (≥50% seizure reduction) with a mean daily dose of 10.6 ± 2.3 mg/day [27]. The response rate (≥50% seizure reduction) in our study was slightly lower than those in the previous studies, which could be explained by the relatively lower mean daily dose of 4.8 mg/day than those in the other study groups. Several recent studies supported the positive association between the dose and efficacy of PER [28,29]. In fact, the mean daily dose in the responder group patients who achieved ≥ 50% seizure reduction in this study was slightly higher than that in the non-responder group (5.3 vs. 4.4, P = 0.04).

Sixty patients among 108 patients maintain the daily PER dose ≤ 4 mg and nineteen of them (37%, 19/60) were responders in this study. Comparing to previous reports, more patients were treated with lower dose of 1 to 4 mg. De Liso et al. [18] reported that 12 patients are treated with 1 to 4 mg among 62 patients who enrolled in multicenter observational study. In a recent retrospective study in Korea, Youn et al. [30] reported only seven patients maintain the daily PER dose of 1 to 4 mg and showed ≥ 50% seizure reduction among 81 enrolled patients, showing that our results were not explained by difference in ethnic groups. The patients in this study had already used more AEDs (mean, 3.8; median, 4; maximum, 7; minimum, 2; interquartile range, 3 to 4) than

### Table 3. Comparison of the clinical factors between adverse event present and adverse event absent group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adverse event present (n = 34, 31.4%)</th>
<th>Adverse event absent (n = 74, 59.6%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>17 (50)</td>
<td>47 (63.5)</td>
<td>0.18</td>
</tr>
<tr>
<td>Age at the start of PER (yr)</td>
<td>21.9 ± 5.5</td>
<td>19.4 ± 4.6</td>
<td>0.16</td>
</tr>
<tr>
<td>No. of concomitant AEDs</td>
<td>3.7 ± 1.1</td>
<td>3.9 ± 1.0</td>
<td>0.50</td>
</tr>
<tr>
<td>Any EIAEDs</td>
<td>15 (44.1)</td>
<td>33 (44.6)</td>
<td>0.99</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>10 (29.4)</td>
<td>23 (31)</td>
<td>0.90</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>6 (17.6)</td>
<td>8 (10.8)</td>
<td>0.43</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>1 (2.9)</td>
<td>1 (1.4)</td>
<td>0.46</td>
</tr>
<tr>
<td>Maintenance dose of PER (mg/day)</td>
<td>4 ± 2.3</td>
<td>5.1 ± 2.2</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean±standard deviation.

PER, perampanel; AED, antiepileptic drug; EIAED, enzyme-inducing antiepileptic drug.
other groups (De Liso et al. [18]: mean, 2.48; Youn et al. [30]: median, 3; maximum, 6; minimum, 1; interquartile range, 3 to 4) and it suggests the high intractability of the patients enrolled in this study. Despite of the intractability of our patient group, low dose of PER was effective in many of them. Recently, some authors suggested that the response rate do not appear to clearly correlate with PER daily dose and some patients can show response at low doses [31,32]. Our findings also support these opinions.

The duration of PER treatment was much longer in the responder group than non-responder group (13.5 months vs. 8.7 months, P = 0.03). This difference could be explained by that there were much more patients who decided PER discontinuation in non-responder group (30 vs. 4, P = 0.00). There was no statistical difference in any other clinical factors between the responders and non-responders, including sex, age at seizure onset, duration of epilepsy, number of concomitant AEDs, concomitant EIAEDs and adverse events (%).

In fact, the patients who were started on PER (n = 10) as the third AED showed a better response rate (50%) than that in the other patients. A previous study also reported a better response rate in the patients in whom PER was added early (after ≤ 2 prior AEDs; 72% were seizure-free) than that in patients in whom PER was added later (≥ 3 prior AEDs; 52% were seizure-free) [33].

The overall adverse event rate was 31.5% (34/108), which is much lower than that reported in previous studies and can also be explained with the lower mean daily dose. Nevertheless, some patients showed psychiatric adverse events at a dose of only 2 mg and eventually stopped taking the drug. The neuropsychiatric symptoms comprised 87% of all adverse events. The occurrence of psychiatric and neurologic symptoms after PER add-on was the main reason for drug withdrawal or dose reduction [22,23,30,34]. However, almost every patient who experienced psychiatric adverse events showed improvement in the symptoms after withdrawal of the drug or dose reduction. The clinical factors associated with the adverse events after addition of PER are not fully understood [30,34]. There were no contributing factors for adverse events, including sex, age, and number of concomitant AEDs and EIAEDs when comparing the adverse event present group with adverse event absent group.

PER is known to be extensively metabolized by the hepatic CYP3A4. Concomitant drugs that modulate CYP3A4 activity can reduce the half-life of PER by 50% to 70%, resulting in lower PER serum concentrations [13,29,35]. However, EIAEDs had no significant effects on the efficacy and adverse event rate in this study. The interpersonal difference in the enzyme activity according to inherited genetics and use of other concomitant drugs can be considered. Further studies monitoring the serum concentration and CYP3A4 genetics could help find the optimal dose titration of PER.

There are some limitations of this study, including the retrospective design, the lack of seizure frequency data according to seizure types, and variable dose titration schedules. However, this study showed that low-dose PER is effective in patients with childhood-onset intractable epilepsy with good tolerability. Further, well-designed prospective study monitoring the serum concentration of PER can help determine the proper dose of PER in children and young adults with intractable epilepsy.

In conclusion, we demonstrated that PER is reasonably effective and tolerable in patients with refractory childhood-onset epilepsy. Tolerable low dose PER can be another choice for patients with intractable epilepsy.

Conflicts of interest

No potential conflicts of interest relevant to this article were reported.

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References


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Isolated Unilateral Sixth Nerve Palsy as the First Manifestation of Multiple Sclerosis

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Clinical features of multiple sclerosis (MS) vary widely depending on the area of the lesions. Although brainstem lesions are common in MS, isolated cranial nerve palsies are rare, especially as an initial manifestation [1]. Among the cranial nerves, the fifth nerve is most commonly involved, followed by the 7th, 6th, 3rd, and 8th nerves at MS [1]. Sixth nerve palsy results in ipsilateral horizontal gaze palsy. Common ocular motor symptoms in MS include nystagmus and internuclear ophthalmoplegia (INO) [2]. Unusual ocular motor findings including bilateral 3rd nerve palsy, opsoclonus, and isolated 6th nerve palsy had been reported in MS patients [2]. Here we report the case of a 15-year-old patient who presented with diplopia due to unilateral 6th nerve palsy as the first manifestation of MS.

A 15-year-old man presented with diplopia for 6 days. Physical examination showed limited abduction of the right eye on right lateral gaze. Adduction of the left eye on right lateral gaze was normal (Fig. 1). Other neurological and blood test findings were normal. Magnetic resonance imaging (MRI) of the brain demonstrated multiple ovoid lesions in the periventricular white matter, cerebellum, corpus callosum, basal ganglia, thalamus, pons, and midbrain as a T2 high-signal intensity (Fig. 2). Both gadolinium-enhancing (Fig. 21) and non-enhancing lesions were present. The lesion in the right pons, which might be in the right sixth cranial nerve pathway, innervated the ipsilateral lateral rectus muscle and might have caused the limited abduction of the ipsilateral eye (Fig. 2B, arrow). MRI of the spine demonstrated T2 hyperintensity and heterogeneous enhancement of the lesions at C4 and C6 (Fig. 2G, H, and J). These findings demonstrated dissemination in time and space. Cerebrospinal fluid (CSF) showed a white blood cell count of 12/mm³ (lymphocyte 99%), 27.9 mg/dL protein, 65 mg/dL glucose, and no bacteria, malignant cells, or oligoclonal bands. CSF immunoglobulin G was elevated (1.95), and antibodies to aquaporin 4 were absent. This patient was not tested antibodies against myelin oligodendrocyte glycoprotein. Ophthalmologic examinations including fundus examination, optical coherence tomography, visual evoked potential, and visual acuity showed normal findings. Brainstem auditory evoked potential and upper and lower extremity somatosensory evoked potentials were normal.

Based on the 2017 McDonald criteria, the patient was diagnosed with MS; one attack and two or more lesions on MRI demonstrating dissemination in time and space. He was treated with intravenous (IV) methylprednisolone (1 g/day) for 5 days, which he did not respond to, followed by oral prednisone (1 mg/kg/day, ta-
pered over 5 weeks). Therefore, IV immunoglobulin (2 g/kg divided over 4 days) was administered, but the lateral rectus muscle dysfunction did not improve. Subsequently, he received a plasma exchange five times in 10 days and had marked improvement in diplopia and the lateral rectus muscle function; Grading of abduction was improved from –4 (no movement beyond the midline) to –1 (75% of movement remains). He has been receiving interferon-β 1b subcutaneously since the 5 days after the last plasma exchange. Interferon-β 1b was titrated to 0.25 mg (8 million IU) every other day. At the 7-month follow-up, the 6th cranial nerve palsy had completely resolved. No neurological symptoms had occurred until the 14-month follow-up. Follow-up MRIs of the brain and spine revealed a slight decrease in the lesion size.

Fig. 1. Ocular motility photography. Test of ocular motility demonstrated limited abduction of the right eye at right gaze (A), esotropia of the right eye at primary position (B), and normal ocular motility at left gaze (C). The consent was obtained from the patient and the guardians regarding the publication of the patient’s images.

Fig. 2. Magnetic resonance imaging (MRI) of the brain demonstrates multiple ovoid lesions in the cerebellum (A), pons (B, arrow), midbrain (C), basal ganglia, thalamus (D), and periventricular white matter (E, F), as a T2 high-signal intensity. MRI of the spine demonstrates T2 hyperintense and heterogeneous enhancing lesions at C3, C4, C6 (G) and T7 (H). MRI of gadolinium-enhanced T1-weighted images demonstrates several lesions in the frontal lobe (I) and C4 (J).
of cases [3]. INO is an eye movement disorder caused by a lesion of the medial longitudinal fasciculus (MLF), which affects conjugate eye movement by connecting the paramedian pontine reticular formation (PPRF)—abducens nucleus complex of the contralateral side to the oculomotor nucleus of the ipsilateral side [3]. The MLF lesion impairs the adduction of the affected eye during contralateral gaze, while the contralateral eye abducts but is accompanied by nystagmus. If the lesion is located in the PPRF, abducens nucleus, or contralateral MLF, conjugate horizontal gaze palsy to the ipsilateral side occurs instead of ipsilateral lateral gaze palsy.

Our patient presented with limited abduction of the unilateral eye and intact conjugate adduction of the contralateral eye. This indicated that the pathologic lesion involved the 6th nerve alone, and not the abducens nucleus, PPRF, or MLF [4]. Isolated 6th nerve palsies are rare, seen only in 0.4% to 1.0% of MS [1]. There have been no reports of isolated sixth nerve palsies in children, so they might be even rarer.

After MS diagnosis, aggressive acute management including steroid, immunoglobulin, and plasma exchange was provided in a timely manner, leading to complete resolution of the 6th nerve palsy. Interferon-β was initiated in the early period and has been maintained without complications and relapses.

Incomplete recovery indicates poor prognosis, and early, effective treatment of MS prevents irreversible long-term complications [5]. Although isolated 6th nerve palsies are rarely observed in MS, especially in children, MS should be a differential diagnosis.

Conflicts of interest

No potential conflicts of interest relevant to this article was reported.

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References

Aseptic Meningitis Accompanied with Kikuchi–Fujimoto Disease

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Kikuchi-Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis, is a rare disease first reported in 1972 by Kikuchi [1] and Fujimoto et al. [2]. KFD is more common in young females under 30 years of age. It is a self-limited disease characterized by cervical lymphadenopathy. Headache accompanied by fever is a common symptom of this disease; however, the central nervous system (CNS) can also be involved. We describe a KFD patient with aseptic meningitis who had a headache as the first symptom of aseptic meningitis.

An 8-year-old boy presented with a 2-day history of fever and a nodule on the right side of the neck. At admission, he had a fever with a temperature of 38.5°C. Physical examination showed multiple tender cervical lymph nodes with a swelling 2 to 3 cm in size on the right side of the neck. Neck movement was not limited. No abnormal neurological signs and symptoms were observed. The patient was discharged with a diagnosis of cervical lymphadenitis.

A week later, the patient was readmitted with fever and pain on the right side of the neck. There were no abnormal neurological symptoms and neurological examination was normal. Laboratory tests on admission showed normal results. C-reactive protein level was 4.4 mg/dL (0 to 0.5). On the second day of readmission, a biopsy of the cervical lymph node was performed. The histopathology was consistent with KFD (Fig. 1). The patient was treated with supportive care including nonsteroidal anti-inflammatory drugs (NSAIDs) administration. General condition improved after 5 days and he was discharged.

Three days after the second discharge, he complained of fever and headache. The body temperature was 38.9°C. The headache was in the forehead region, 6-point on the numerical pain rating scale, and alleviated with the administration of NSAIDs. No fever was observed after regular NSAIDs administration for every 8 hours. However, on the 6th day of admission, the headache aggravated severely, and the patient could not speak for a few seconds due to pain. Meningeal irritation signs were positive on neurological examination. The cerebrospinal fluid (CSF) opening pressure measured at lumbar puncture was 20 cm of water (<18 cm H2O). CSF was clear with a red blood cell count of 2/μL, white blood cell count of 33/μL (0 to 5), glucose concentration of 67 mg/dL (simultaneously sampled blood sugar, 119 mg/dL), plasma glucose ratio of 0.56, and protein concentration of 47 mg/dL (15 to 45). CSF culture for bacteria was negative. Three days later, polymerase chain reaction for
herpes simplex virus was reported as negative. On the 6th day of the third admission, magnetic resonance imaging of the brain with diffusion-weighted image showed no significant abnormalities. Since the CSF opening pressure was elevated, we started mannitol administration. After 3 days, the clinical symptoms improved and mannitol administration was stopped. Twelve days after the admission, the patient was discharged with no fever or headache. The lymph node size decreased to less than 1 cm. Since discharge, the follow-up has been conducted for about a year in our outpatient clinic, and no identical symptoms have been observed.

KFD is a rare and self-limited disease. Due to its self-limiting nature, KFD is frequently misdiagnosed and comorbidities can be easily overlooked. About 5% to 10% of the KFD patients showed central nervous CNS complications, which are resolved without any treatment [3,4]. Out of the 244 KFD patients analyzed by Sato et al. [3], 11 patients (5%) showed neurological involvement such as aseptic meningitis, mono-neuritis multiplex, hemiparesis, brachial neuritis, and photophobia.

Kucukardali et al. [4] reported aseptic meningitis in 9.8% of the 41 KFD patients studied. Noursadeghi et al. [5] reported a case of Kikuchi’s disease with aseptic meningitis in a 57-year-old female and successfully treated it with corticosteroids alone. The authors suggested that a low dose of corticosteroid could shorten the duration of the illness. In our case, the patient’s symptom relieved with mannitol only, but if the symptoms last even after mannitol administration, systemic steroid administration could be an option.

Although headache with fever is a common symptom in KFD, it can also be a symptom of meningitis. Given the fact that about 10% of the KFD cases show CNS involvement and that the disease is self-limited [3,4], we could make an early decision for further evaluation and treatment of a KFD patient with a severe headache. In such cases, early consideration of the possibility of aseptic meningitis can be helpful in the assessment and in the timely treatment of the disease.

Conflicts of interest

No potential conflicts of interest relevant to this article were reported.

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References

Atypical Benign Partial Epilepsy of Childhood Treated with Prednisolone and Ethosuximide

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Atypical benign partial epilepsy (ABPE) is a complicated form of benign epilepsy with centrotemporal spikes (BECTS) [1]. It is characterized by an earlier age of onset, multiple seizure types including epileptic negative myoclonic, atonic, and atypical absence seizures, as well as focal motor seizures [2]. Electroencephalography (EEG) depicts frequent centrotemporal spikes that are activated during sleep, and similar continuous spike and wave during slow wave sleep (CSWS), but it does not fulfill the standard criteria for CSWS [3]. It has recently been suggested that ABPE is a component of the epilepsy-aphasia spectrum that includes some disorders ranging in severity, where BECTS occurs at the mild end of the spectrum and the severe end includes Landau-Kleffner syndrome and epileptic encephalopathy with CSWS [3]. Patients with ABPE usually exhibit normal neurologic and mental functions through the course, and favorable outcomes [2]. Notably however, some patients reportedly experience cognitive decline, language impairment, and motor skill regression [1,4]. This report describes a boy with ABPE who underwent a very active seizure period accompanied by regression of motor skills, speech, and cognitive function, that was ultimately controlled via ethosuximide and prednisolone.

A 3-year-old boy was referred to our clinic for evaluation of focal motor seizures characterized by jerking of his right arm and leg, facial twitching, and drooling during sleep. He had no remarkable medical history. There was no known family history of epilepsy. His developmental milestones were reportedly normal, which was categorized into peer or high-level group over all areas including gross motor, fine motor, cognition, communication, social interaction, and self-control by the Korean Developmental Screening Test. Physical examination and brain magnetic resonance imaging results were normal. EEG depicted high-voltage and biphasic sharp waves activated by sleep in the left centrotemporal area with normal background (Fig. 1A). The electro-clinical diagnosis was BECTS. Over the following year, while being treated with oxcarbazepine, levetiracetam, and nighttime clobazam, facial and lip clonic seizures continued to occur every 1 or 2 weeks. From the age of 4 years he experienced recurrent bilateral tonic-clonic seizures or hemiclonic seizures of the right arm and leg, with Todd paralysis upon waking. Oxcarbazepine, levetiracetam, and clobazam were discontinued because his seizures were controlled after the addition of valproic acid. Interictal EEG depicted typical rolandic spikes.

This study was approved by the Institutional Review Board (IRB) of Yonsei University (IRB no., 19-0010). Informed consent was waived due to the retrospective nature of the study.

At the age of almost 5.5 years, drop attacks de-
veloped with staring, frequent falls, and an unsteady gait. Duration of seizure was short in less than a minute, and there was no postictal drowsiness. He exhibited slurred speech, dysarthria, and dysphagia with drooling. Sleep EEG depicted continuous high amplitude asymmetric spike-and-wave discharges, predominantly in the left centrotemporal area, similar to CSWS (Fig. 1B). Assessment via the Preschool Receptive-Expressive Language Scale and Korean-Child Development Inventory revealed that his development was severely delayed in all domains except for fine motor area (Fig. 2). His equivalent developmental age with regard to receptive language was 43 months, for expressive language it was 40 months, and his integrated developmental age was 2 years and 9 months. Oral prednisolone (2 mg/kg/day) combined with ethosuximide (20 mg/kg/day) was added to valproic acid. His motor skills, language, and seizures started to improve rapidly. Surprisingly, at a follow-up examination 4 weeks later EEG revealed no abnormal epileptic discharges (Fig. 1C). Prednisolone was slowly tapered off, and it was discontinued after 2 months.

At age 8 years, he remains seizure-free with ethosuximide and valproic acid. He continues to yield normal neurologic examination results, and is attending elementary school. EEG depicts focal spikes in the left centrotemporal areas (Fig. 1D). His results in the Korean Wechsler Intelligence Scale for Children (K-WISC-IV) revealed a borderline full-scale intelligence quotient (IQ) of 74 (verbal comprehension 80, perceptual reasoning 91, working memory 70, processing speed 76).

Diagnostic exome sequencing was performed to detect potentially genetic causes of ABPE. The heterozygous missense variant of GABRA1 (NM_000806: c.529G > A) was detected, and was confirmed via direct sequencing. Segregation analysis revealed that the GABRA1 variant was paternally inherited.

In the current patient, clinical seizure history and EEG findings suggest ABPE [3]. Although we could not acquire ictal EEG and electromyography data from the patient, the semiology of seizures such as the sudden drop attacks and frequent staring with no response to stimuli suggest epileptic negative motor and atypical absence seizures, which are primary components of ABPE semiology. EEG depicted sleep activation of focal epileptiform discharges.
Assessment with Korean-Child Development Inventory (K-CDI) revealed severe delay in all developmental domains except for fine motor area.

Fig. 2. Assessment with Korean-Child Development Inventory (K-CDI) revealed severe delay in all developmental domains except for fine motor area.
with asymmetric continuous spike-and-wave activity during sleep. The patient exhibited cognitive regression in conjunction with active epilepsy. We did not detect any meaningful genetic variants in the present patient. Recent identification of GRIN2A variants in a small subset of epilepsy-aphasia spectrum patients is notable; however, the associated phenotypic expression is evidently highly variable and may be affected by multiple genes or gene modifiers [1,4].

The current patient’s seizures were resistant to various antiepileptic drugs, but his epilepsy and cognitive function improved after the addition of ethosuximide and prednisolone, which have previously been reported to be effective in ABPE [1,5]. The mechanism by which ethosuximide affects neuronal excitability is considered to involve blockage of T-type calcium channels in thalamic neurons and the corresponding cortex [5]. Therefore, the dramatic effects of ethosuximide may be due to unique antiepileptic effects on epileptic networks in both the thalamus and sensorimotor cortex, but the exact mechanisms remain to be elucidated [5]. In patients who do not respond to antiepileptic drug therapy, corticosteroid administration should be considered in order to prevent language disturbance [1,5]. Steroids and some other immunomodulating therapies are also reportedly effective in ABPE, suggesting that the immune system may be involved in the pathophysiology of ABPE [1,2,5].

In conclusion, ABPE is a distinctive epileptic syndrome characterized by early onset, typical rolandic seizures followed by negative motor seizures, and aggravation to diffuse and continuous epileptic discharges on EEG. Ethosuximide and steroid are effective and safe for the treatment of ABPE, and should be considered relatively early in the course of disease, particularly given the potential for the preservation of intellectual functioning associated with early intervention.

Conflicts of interest
No potential conflicts of interest relevant to this article were reported.

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References
Instructions to authors

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General information

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