Aims and scope

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Clinical Features and Treatment Efficacy in CDKL5 Mutation-Related Epileptic Encephalopathy in the Infant

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Purpose: Mutations in the cyclin-dependent kinase-like 5 (CDKL5) gene are associated with epileptic encephalopathy and severe cognitive impairment. We aim to characterize the association between this gene and treatment efficacy.

Methods: We retrospectively analyzed 10 patients who were treated at Severance Children’s Hospital for epileptic encephalopathy who were subsequently diagnosed with a CDKL5 mutation using next-generation sequencing.

Results: Electroencephalography (EEG) results showed generalized pattern abnormalities in 60% (6/10) of patients with CDKL5 mutations. We analyzed the effects of three treatments, namely antiepileptic drugs (AEDs), ketogenic diet (KD), and steroids. A more than 50% reduction in seizures was observed in 12% (1/8) of patients treated with clobazam. KD treatment proved ineffective in most cases. In addition, a more than 50% reduction in seizures was observed in 57% (4/7) of patients treated with steroids. EEG analysis of patients treated effectively with steroids revealed that 75% (3/4) showed hypsarrhythmia and 25% (1/4) showed focal epileptiform.

Conclusion: In this study, as in other studies, AEDs and KD did not effectively control seizures in most patients with a CDKL5 mutation. However, steroid therapy reduced the frequency of seizures in patients who also exhibited hypsarrhythmia. This suggests that steroid treatment is helpful in cases of hypsarrhythmia with CDKL5 mutations.

Keywords: Spasms, infantile; CDKL5 deficiency disorder; Epilepsy; Epileptic encephalopathy

Introduction

Mutations in the cyclin-dependent kinase-like 5 (CDKL5) gene are associated with severe cognitive impairments and early epileptic encephalopathy, such as infantile spasms. These mutations are mainly expressed in women [1,2]. Accordingly, the CDKL5 mutation was found in two female patients with severe cognitive impairment with an infantile spasm in 2003 [1]. The CDKL5 mutation has been reported in atypical Rett syndrome patients who report having seizures before 6 months of age [2,3]. However, unlike patients with typical Rett syndrome who had epileptic seizures before 3 years of age, those with CDKL5 mutations, on average, reported seizures 4 months earlier, and in many cases, lacked typical Rett syndrome features [3-5]. In 2013, Fehr et al. [6] reported that the CDKL5 mutation should be classified as an independent early epileptic encephalopathy, not atypical Rett syndrome. Seizures...
with CDKL5 mutations in early infancy are typically characterized by tonic seizures or muscle contractions with vibration, followed by a clonic phase with a series of spasms that gradually turn into rhythmic distal myoclonic jerks [7]. There is, however, no characteristic electroencephalography (EEG) pattern in patients with a CDKL5 mutation [7-10]; EEG can present, initially, as normal background activity in patients with this mutation [9,10]. Although patients with CDKL5 mutations show a transient response to various antiepileptic drugs (AEDs), they are generally difficult to treat and are unresponsive to most intractable epilepsy treatment [11].

The purpose of this study was to analyze the characteristics of CDKL5 mutations in patients from a single center, as well as to confirm the efficacy of therapy.

Materials and Methods

We retrospectively analyzed 10 patients with CDKL5 pathogenic mutations, diagnosed at Severance Children’s Hospital, Seoul, South Korea. Patients were reassessed at every outpatient clinic. The patient’s response to the drug was categorized into four groups: (1) patient was seizure free for more than 6 months; (2) seizures were reduced by more than 50%; (3) seizures were reduced by less than 50%; or (4) no effect. If the patient does not affect the clinical symptoms, the drug or treatment method will be added or changed. In this case, we have assessed the treatment methods and drugs we want to investigate. In this study, when steroid was chosen as treatment options, we prescribed prednisolone. It was used at 40 to 60 mg/day for 2 weeks and then tapered off for 2 weeks [12,13].

All children underwent several analyses, including next-generation genetic sequencing, routine EEG recordings, and video EEG recordings. The EEG terminology used in this study is based on a paper published by Kane et al. [14] in 2017.

Genomic DNA extracted from all individual samples was used for library preparation and target capture using custom panels targeting candidate genes. The databases used for analysis and mutation analysis include online Mendel inheritance, Human Gene Mutation Database, ClinVar, dbSNP, 1000 Genome, Exome Aggregation Consortium, Exome Sequencing Project, and Korean Reference Genome Database. All pathogenic and possible pathogenic variants were identified by Sanger sequencing. All patients underwent video EEG recording at the first evaluation and routine EEG recording at the follow-up evaluation. Routine EEG recordings were performed for an average of 30 minutes and video EEG recordings were performed for more than 4 hours. Scalp electrodes were placed according to the International 10–20 system.

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.

Results

We identified a CDKL5 pathogenic mutation in 10 patients (eight women, two men). Amongst all patients, the average age at seizure onset was 3.6 months (range, 0.6 to 11). Six patients with the mutation demonstrated generalized abnormalities in the first EEG recording; two patients showed hypsarrhythmic patterns, one showed EEG suppression patterns, two patients showed generalized sharp and wave discharges, and one patient showed generalized slow and disorganized background abnormalities. In total, four patients showed hypsarrhythmic patterns during the study period. Three patients demonstrated regional epileptiform discharges and one patient demonstrated regional paroxysmal fast activities on EEG. All patients exhibited motor seizures and six patients exhibited spasms. One of the patients who exhibited spasms did not show subsequent motor seizure. Brain magnetic resonance imaging data appeared normal in most cases, and we found no focal abnormalities. There was a significant delay in cognition in nine of the 10 patients who underwent cognitive testing. Details on genetic and clinical features of patients can be found in Tables 1 and 2.

We compared the effects of AEDs such as valproic acid (VPA), clobazam (CLB), and vigabatrin (VGB) on seizures. Additionally, we evaluated the effects of steroids and ketogenic diets (KDs) on seizures. Eight of the 10 patients used VPA, six of whom reported no effects, and two reported a less than 50% reduction in the frequency of seizures. Nine patients used CLB, four of whom had a less than 50% seizure reduction, three had no effect, and one had a more than 50% seizure reduction. Seven patients used VGB, five of whom reported no effects, and two reported a less than 50% re-

### Table 1. Genetic features of 10 patients with CDKL5 mutation

<table>
<thead>
<tr>
<th>Pt</th>
<th>Inheritance</th>
<th>CDS/amino acid change</th>
<th>Type of mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>c.2354dupA, p.Lys786GlufsTer15</td>
<td>Frameshift duplication</td>
</tr>
<tr>
<td>2</td>
<td>De novo</td>
<td>c.511T&gt;A, p.Tyr171Asn</td>
<td>Missense</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>c.978-1G&gt;A</td>
<td>Splicing</td>
</tr>
<tr>
<td>4</td>
<td>De novo</td>
<td>c.282+1G&gt;A</td>
<td>Splicing</td>
</tr>
<tr>
<td>5</td>
<td>De novo</td>
<td>c.175C&gt;T, p.Arg59Ter</td>
<td>Nonsense</td>
</tr>
<tr>
<td>6</td>
<td>De novo</td>
<td>c.513C&gt;T, p.Tyr171Ter</td>
<td>Nonsense</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>c.458A&gt;T, p.Asp153Val</td>
<td>Missense</td>
</tr>
<tr>
<td>8</td>
<td>De novo</td>
<td>c.145+2T&gt;A</td>
<td>Splicing</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>c.403+1G&gt;A</td>
<td>Splicing</td>
</tr>
<tr>
<td>10</td>
<td>De novo</td>
<td>c.146-1G&gt;T</td>
<td>-</td>
</tr>
</tbody>
</table>
duction in the frequency of seizures. Eight patients were on KDs, seven of whom reported no effect and only one of whom had a less than 50% reduction in the frequency of seizures (Table 3). In addition, seven patients used steroids, one of whom reported no seizures for more than 6 months, and three of whom reported a reduction in frequency of seizures by more than 50%. EEG results in the patient who remained seizure-free for more than 6 months showed regional epileptiform when seizures first occurred (age, 0.6 months), but no slowing pattern. These three patients under steroids with a reduction of more than 50% in the frequency of seizures showed hypsarrhythmia on EEG.

**Discussion**

Patients with a CDKL5 mutation often present with epileptic encephalopathy, which is a challenging condition to treat, and has been reported to be only temporarily affected by AEDs [11,15,16]. Therefore, the treatment goal for these patients involves improving their quality of life and achieving, at minimum, a slight reduction in the frequency of seizures [11]. CDKL5 mutation is a causative mutation of infantile spasm, so treatment with steroid has also been tried in some cases [12,13,15]. One study reported that seizures were not completely abolished in patients with CDKL5 mutations, but KD and some drugs, such as VGB, have helped to reduce the frequency of seizures [15,16].

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex</th>
<th>sz onset age (mo)</th>
<th>ECD</th>
<th>sz type</th>
<th>1st EEG finding</th>
<th>Age at 1st Hyps (mo)</th>
<th>Brain MRI</th>
<th>Cognitive function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>11</td>
<td>WS, LGS</td>
<td>Spasm</td>
<td>Generalized sharp and wave discharges</td>
<td>19</td>
<td>NL</td>
<td>Significantly delayed</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>3</td>
<td>WS</td>
<td>Spasm</td>
<td>Normal</td>
<td>-</td>
<td>NL</td>
<td>Significantly delayed</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>1.7</td>
<td>EIIE</td>
<td>Myoclonic</td>
<td>Suppression burst</td>
<td>-</td>
<td>NL</td>
<td>Significantly delayed</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>1</td>
<td>WS, LGS</td>
<td>Spasm</td>
<td>Hyps</td>
<td>3</td>
<td>NL</td>
<td>Significantly delayed</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>5</td>
<td>WS, LGS</td>
<td>Spasm</td>
<td>Hyps</td>
<td>5</td>
<td>NL</td>
<td>Significantly delayed</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>5</td>
<td>WS</td>
<td>Spasm</td>
<td>Generalized slow and disorganized background activities</td>
<td>9</td>
<td>NL</td>
<td>Significantly delayed</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>3</td>
<td>LGS</td>
<td>Spasm</td>
<td>Generalized sharp and slow wave</td>
<td>-</td>
<td>Atrophy</td>
<td>Significantly delayed</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>0.6</td>
<td>EME</td>
<td>Myoclonic</td>
<td>Regional sharp wave and regional paroxysmal fast activities</td>
<td>-</td>
<td>NL</td>
<td>Significantly delayed</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>4</td>
<td>Focal epilepsy</td>
<td>Focal motor</td>
<td>Regional slowing</td>
<td>-</td>
<td>Atrophy</td>
<td>Significantly delayed</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>2</td>
<td>Focal epilepsy</td>
<td>GTC</td>
<td>Regional sharp wave discharges</td>
<td>-</td>
<td>NL</td>
<td>-</td>
</tr>
</tbody>
</table>

EEG, electroencephalography; CDKL5, cyclin-dependent kinase-like 5; Pt, patients; sz, seizure; ECD, electroclinical diagnosis; Hyps, hypsarrhythmia; MRI, magnetic resonance imaging; WS, West syndrome; LGS, Lennox-Gastaut syndrome; NL, normal; EIIE, early infantile epileptic encephalopathy; EME, early myoclonic encephalopathy; GTC, generalized tonic-clonic.

<table>
<thead>
<tr>
<th>Pt</th>
<th>Hyps</th>
<th>Generalized Patter EEG</th>
<th>Baseline sz freq</th>
<th>VPA</th>
<th>CLB</th>
<th>VGB</th>
<th>Steroid</th>
<th>KD</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>Daily</td>
<td>Less than 50%</td>
<td>No effect</td>
<td>No effect</td>
<td>More than 50%</td>
<td>No effect</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>2 times/wk</td>
<td>No effect</td>
<td>Less than 50%</td>
<td>Less than 50%</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>+</td>
<td>Daily</td>
<td>Less than 50%</td>
<td>Less than 50%</td>
<td>Less than 50%</td>
<td>-</td>
<td>No effect</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td>Daily</td>
<td>No effect</td>
<td>Less than 50%</td>
<td>No effect</td>
<td>More than 50%</td>
<td>No effect</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>+</td>
<td>Daily</td>
<td>No effect</td>
<td>-</td>
<td>Less than 50%</td>
<td>More than 50%</td>
<td>No effect</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>+</td>
<td>Daily</td>
<td>No effect</td>
<td>Less than 50%</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>-</td>
<td>3 times/wk</td>
<td>No effect</td>
<td>No effect</td>
<td>-</td>
<td>sz free more than 6 mo</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>Daily</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>sz free more than 6 mo</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>-</td>
<td>Daily</td>
<td>No effect</td>
<td>More than 50%</td>
<td>-</td>
<td>-</td>
<td>No effect</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>-</td>
<td>Daily</td>
<td>No effect</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

CDKL5, cyclin-dependent kinase-like 5; Pt, patients; Hyps, hypsarrhythmia; EEG, electroencephalography; sz, seizure; freq, frequency; VPA, valproic acid; CLB, clobazam; VGB, vigabatrin; KD, ketogenic diet.
In the current study, we investigated 10 patients with the CDKL5 mutation, who were being treated with VPA (n = 8), CLB (n = 8), and/or VGB (n = 7). Five patients were being treated with a combination of all three drugs. Except for one patient who showed a more than 50% reduction in the frequency of seizures on CLB, most drugs yielded a less than 50% reduction in the frequency of seizures. There was no effect in six of the eight patients on VPA, and five of the seven patients on VGB. With CLB, however, only three of the eight patients reported no effect, four patients reported a less than 50% reduction, and one patient reported a less than 50% reduction. Based on these findings, CLB seems to be the most effective among the three drugs in reducing seizures.

We also studied the effect of a KD on seizure reduction. Eight patients were on a KD, and seven of them did not show any reduction in seizures. This seems to be different from previous studies that ketone-producing diets are most helpful in reducing the frequency of seizures [15]. However, this study has been studied with a small number of patients, so further studies are needed.

Seven patients were treated with steroids for seizure control. One of them maintained a seizure-free condition for more than 6 months, and three patients reported a more than 50% reduction in seizures. EEG results showed that four patients had hypsarrhythmia, three of whom also demonstrated a more than 50% reduction in seizures under steroid therapy. This suggests that steroid, a treatment option for infantile spasm, can also be a good treatment option for patients with CDKL5 mutations when they present with hypsarrhythmic EEG.

Contrary to previous studies, the AED and KD were not effective in CDKL5 mutation patients. However, in the case of hypsarrhythmic pattern on EEG, the steroid treatment showed a more than 50% seizure reduction effect (three-fourths). Currently, steroid therapy for infantile spasm is widely used and proven effective [12,13]. This study suggests that steroid treatment can also be helpful in cases of infantile spasm with a CDKL5 mutation who have a hypsarrhythmic EEG.

Due to the small number of patients included in this study and the limitations of the retrospective study, it is difficult to obtain reliable results, and some results show different results from previous studies. So, further studies will be needed in the future. In addition, this study evaluated the correlation with only interictal EEG pattern. This is also a limitation of this study and further research is needed.

Conflicts of interest

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

Acknowledgements

This study was supported by a faculty research grant of Yonsei University College of Medicine (6-2015-0140).

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant number: HI18C0586).

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References


Purpose: Cytokines demonstrate active roles in the occurrence of febrile seizures (FS). However, whether a genetic predisposition to inflammation is implicated in FS, febrile seizure plus (FS+) or genetic epilepsy with febrile seizure plus (GEFS+) is still unclear. Therefore we perform this study to find the association of promotor variants in pro-inflammatory cytokine tumor necrosis factor-α (TNF-α) genes and anti-inflammatory cytokine interleukin 10 (IL-10) genes either with FS, FS+, and GEFS+ in Korean children.

Methods: Fifty-seven children with FS, 32 FS+, and 12 GEFS+ patients were compared with 108 controls. The allelic and genotypic distributions were compared for TNF-α -238 (rs361525), -308 (rs1800629), -857 (rs1799724), -863 (rs1800630), and IL-10 -592 (rs1800872), -819 (rs1800871), -1082 (rs1800895), and -1352 (rs1800893).

Results: Allelic and genotypic frequencies of TNF-α and IL-10 promotor variants showed an association with FS, FS+, and GEFS+ in a recessive mode of inheritance pattern (P<0.05). AA genotypes at TNF-α -863 were present only in controls. However, AA genotypes at TNF-α -863 were present only in controls. TNF-α -863 (rs1800630) promoter variants showed an association with FS, FS+, and GEFS+ in a recessive mode of inheritance pattern (P<0.05).

Conclusion: Our results suggest that AA genotypes at TNF-α -863 may be associated with FS, FS+, and GEFS+, implicating protective roles against to development of FS, FS+, and GEFS+.

Keywords: Tumor necrosis factor-alpha; Interleukin-10; Epilepsy; Seizures, febrile; Variants
Introduction

Febrile seizure (FS) is the most common type of seizure during childhood period, and defined as seizures provoked by fever without central nervous system (CNS) infection [1]. Febrile states are induced by pyrogenic response to various infections, and the magnitude of pyrogenic response influences the body temperature of each child. Interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α) are major pro-inflammatory cytokines controlling pyrogenic actions [2]. Overproduction of pro-inflammatory cytokines can boost pyrogenic action and in some children, therefore body temperatures may overwhelm the seizure threshold, provoking to develop FS.

The association between cytokine genetic variants and susceptibility to FS and epilepsy are still controversial. IL-1β-511 promoter variants were reported to have an association with FS [3,4]. TNF-α-308 genotype showed no significant association with FS in meta-analysis study [5-8]. In other studies, GG genotypes of TNF-α-238 were more prevalent than GA genotype among FS compared to controls in Iranian children [9]. Japanese FS study showed significant lower frequencies of the IL-10-592C/-819C/-1082A haplotype than controls [10]. In contrast, IL-10-592, -819, and -1082 showed no significant allelic association in Iranian FS study [11].

Genetic epilepsy with febrile seizure plus (GEFS+) is a familial disorder with association of FS and epilepsy and shows autosomal dominance inheritance with variable penetrance [12]. And febrile seizure plus (FS+) is a same phenotypic disorder to GEFS+ without family history. To date, sodium voltage-gated channel alpha subunit 1 (SCN1A), sodium voltage-gated channel beta subunit 1 (SCN1B), and gamma-aminobutyric acid type A receptor gamma2 subunit (GABRG2) are known to be disease-causing genes of GEFS+ [13]. Inheritance in GEFS+ is typically autosomal dominant with incomplete penetrance, although other complex inheritance patterns may also occur. However, whether genetic susceptibility to inflammation may be one of the genetic causes for FS or GEFS+ is still unclear.

To determine whether promotor variants of TNF-α and IL-10 influence the susceptibility to FS, FS+, and GEFS+, we analysed genetic variants in the promotor region of TNF-α and IL-10 among children with FS and GEFS+ patients and compared to controls.

Materials and Methods

1. Patient information
Children with FS, FS+, and GEFS+ patients were enrolled in this study from June 2008 to May 2013, visiting the emergency room of Seoul Metropolitan Government Seoul National University Boramae Medical Center with acute seizure attacks. Inclusion criteria for FS were children with seizures associated with fever above 38°C between 6-month-old to 5-year-old, without CNS infection, neurologic deficits and previous afebrile seizures [14]. Diagnosis of genetic epilepsy with febrile seizure plus (GEFSP) followed the criteria established in the 2017 International Classification of Epileptic Syndromes [15]. GEFS+ is usually diagnosed in families whose members have FSs that may continue past the usual age where these are expected to resolve and/or be accompanied by afebrile seizures that may be generalized seizures or focal seizures. FS+ are distinguished from the GEFS+ on the basis of family history. Controls were children matched for age without history of FS nor epilepsy. This study was approved by the Institutional Review Board at the Seoul Metropolitan Government Seoul National University Boramae Medical Center (20080918/06-2008-74/76). Informed consent was obtained from the parent of each child.

2. Variants selection
A total of four variants located in the promotor region of TNF-α, -238 (rs361525), -308 (rs1800629), -857 (rs1799724), -863 (rs1800630), and also four variants located in the promotor region of IL-10, -592 (rs1800872), -819 (rs1800871), -1082 (rs1800896), -1352 (rs1800893), were selected from the dbSNP database (www.ncbi.nlm.nih.gov/SNP) and the HapMap human SNP database (www.hapmap.org). For selecting variants, variants with a minor allele frequency above 0.05 were included. To estimate pairwise linkage disequilibrium of variant marker, we used Haplovıew v4.0 (http://www.broadinstitute.org/haplovıew/haplovıew). All variants did not show the results of the chi-square test to reject the Hardy-Weinberg equilibrium. The default confidence interval algorithm of the Haplovıew program revealed 1 haplotype block (Fig. 1A) of TNF-α-857, -863 and 1 haplotype block (Fig. 1B) of IL-10-592, -819, -1082, -1352, from patient group data.

3. Variant sequencing and genotyping
Probes and primers were designed with genomic sequence information. After amplifying the variant spanning fragments by polymerase chain reaction, genotyping was performed with SNaPshot (Sequenom, San Diego, CA, USA). The person analysing the genotype result was blinded to the clinical data.

4. Statistical analysis
The trend test, chi-square test, Fisher exact test and the logistic regression test were the statistical approaches used analysing the
genotype distributions of patient group including FS, FS+, and GEFS+ and then comparing with controls, depending on mode of inheritance [16], such as additive, dominant and recessive, based on the minor allele of each variants. IBM SPSS statistics version 20 (IBM Co., Armonk, NY, USA) and R version 3.2.5 (http://www.r-project.org) were used to analyse the tests. The statistical significance of differences was set as $P < 0.05$ for all tests.

**Results**

1. **Patient characteristics**

Fifty-seven children with FS, 32 FS+, and 12 GEFS+ patients and 108 controls were enrolled. Semiology of FS were 46 (81%) simple types and 11 (19%) complex types. Three FS children had a history of febrile status epilepticus. All patients with FS+ and GEFS+ developed epilepsy after previous FS attacks. The children with FS, FS+, and GEFS+ patients did not show significant differences by sex, age, and laboratory findings with controls.

2. **TNF-α allele and genotype variants**

AA genotypes at TNF-α-863 were present only in controls. AA genotype at TNF-α-863 showed significant negative association with FS, FS+, and GEFS+ ($P = 0.029$) (Table 1). TNF-α-238, TNF-α-308, and TNF-α-857 showed no significant allelic and genotypic differences (Table 2).

3. **IL-10 allele and genotype variants**

IL-10-592, -819, -1082, and -1352 failed to show significant allelic or genotypic association with FS, FS+, and GEFS+ compared to controls (Table 3 and 4).

4. **Haplotype analysis: TNF-α-857 and TNF-α-863**

Haplotype frequencies of block 1 consisted with TNF-α-863 and TNF-α-857 showed no significant association with patients group of FS, FS+, and GEFS+ compared to controls.

5. **Haplotype analysis: IL-10-592, -819, -1082, and -1352**

Haplotype frequencies of block 1 consisted with IL-10-592, -819, -1082, and -1352 showed no significant association with patients group of FS, FS+, and GEFS+ compared to controls (Table 5).

**Discussion**

This study demonstrates that allelic and genotypic frequencies of TNF-α and IL-10 promotor variants showed no significant differences between FS, FS+, and GEFS+ versus controls in Korean children. However, AA genotypes at TNF-α-863 were present only in controls, therefore AA genotype at TNF-α-863 showed...
Table 1. Comparison of genotypic frequencies of 4 TNF-α SNPs between the patients with FS, FS+, and GEFS+ versus controls

<table>
<thead>
<tr>
<th>Gene variants</th>
<th>Genotype</th>
<th>No. (%)</th>
<th>Genetic mode</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>FS, FS+, GEFS+ (n=100)</td>
<td>Control (n=106)</td>
<td></td>
</tr>
<tr>
<td><strong>TNF-α-238 rs361525</strong></td>
<td>G/G</td>
<td>84 (84.0)</td>
<td>94 (88.7)</td>
<td>Additive</td>
</tr>
<tr>
<td></td>
<td>G/A</td>
<td>16 (16.0)</td>
<td>12 (11.3)</td>
<td>Dominant</td>
</tr>
<tr>
<td></td>
<td>A/A</td>
<td>0 (0.0)</td>
<td>1 (0.9)</td>
<td>Recessive</td>
</tr>
<tr>
<td><strong>TNF-α-308 rs1800629</strong></td>
<td>G/G</td>
<td>85 (85.9)</td>
<td>93 (87.7)</td>
<td>Additive</td>
</tr>
<tr>
<td></td>
<td>G/A</td>
<td>14 (14.1)</td>
<td>12 (11.3)</td>
<td>Dominant</td>
</tr>
<tr>
<td></td>
<td>A/A</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>Recessive</td>
</tr>
<tr>
<td><strong>TNF-α-857 rs1799724</strong></td>
<td>C/C</td>
<td>71 (71.7)</td>
<td>73 (68.9)</td>
<td>Additive</td>
</tr>
<tr>
<td></td>
<td>C/T</td>
<td>24 (24.2)</td>
<td>30 (28.3)</td>
<td>Dominant</td>
</tr>
<tr>
<td></td>
<td>T/T</td>
<td>4 (4.0)</td>
<td>3 (2.8)</td>
<td>Recessive</td>
</tr>
<tr>
<td><strong>TNF-α-863 rs1800630</strong></td>
<td>C/C</td>
<td>69 (69.0)</td>
<td>69 (65.1)</td>
<td>Additive</td>
</tr>
<tr>
<td></td>
<td>C/A</td>
<td>31 (31.0)</td>
<td>31 (29.2)</td>
<td>Dominant</td>
</tr>
<tr>
<td></td>
<td>A/A</td>
<td>0 (0.0)</td>
<td>6 (5.7)</td>
<td>Recessive</td>
</tr>
</tbody>
</table>

*P<0.05.

Table 2. Comparison of allelic frequencies of 4 TNF-α SNPs between the patients with FS, FS+, and GEFS+ versus controls

<table>
<thead>
<tr>
<th>Gene variants</th>
<th>Genotype</th>
<th>No. (%)</th>
<th>Allelic association</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>FS, FS+, GEFS+ (n=100)</td>
<td>Control (n=106)</td>
<td></td>
</tr>
<tr>
<td><strong>TNF-α-238 rs361525</strong></td>
<td>G</td>
<td>184 (92)</td>
<td>200 (94)</td>
<td>0.346</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>16 (8)</td>
<td>12 (6)</td>
<td></td>
</tr>
<tr>
<td><strong>TNF-α-308 rs1800629</strong></td>
<td>G</td>
<td>184 (93)</td>
<td>198 (93)</td>
<td>0.851</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>14 (7)</td>
<td>14 (7)</td>
<td></td>
</tr>
<tr>
<td><strong>TNF-α-857 rs1799724</strong></td>
<td>C</td>
<td>166 (84)</td>
<td>176 (83)</td>
<td>0.824</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>32 (16)</td>
<td>36 (17)</td>
<td></td>
</tr>
<tr>
<td><strong>TNF-α-863 rs1800630</strong></td>
<td>C</td>
<td>169 (85)</td>
<td>169 (80)</td>
<td>0.206</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>31 (15)</td>
<td>43 (20)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Comparison of genotypic frequencies of 4 IL-10 SNPs between the patients with FS, FS+, and GEFS+ versus controls

<table>
<thead>
<tr>
<th>Gene variants</th>
<th>Genotype</th>
<th>No. (%)</th>
<th>Genetic mode</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>FS, FS+, GEFS+ (n=100)</td>
<td>Control (n=106)</td>
<td></td>
</tr>
<tr>
<td><strong>IL-10-592 rs1800872</strong></td>
<td>A/A</td>
<td>54 (54.0)</td>
<td>50 (47.2)</td>
<td>Additive</td>
</tr>
<tr>
<td></td>
<td>A/C</td>
<td>40 (40.0)</td>
<td>49 (46.2)</td>
<td>Dominant</td>
</tr>
<tr>
<td></td>
<td>C/C</td>
<td>6 (6.0)</td>
<td>7 (6.6)</td>
<td>Recessive</td>
</tr>
<tr>
<td><strong>IL-10-819 rs1800871</strong></td>
<td>T/T</td>
<td>54 (54.0)</td>
<td>50 (47.2)</td>
<td>Additive</td>
</tr>
<tr>
<td></td>
<td>T/C</td>
<td>40 (40.0)</td>
<td>49 (46.2)</td>
<td>Dominant</td>
</tr>
<tr>
<td></td>
<td>C/C</td>
<td>6 (6.0)</td>
<td>7 (6.6)</td>
<td>Recessive</td>
</tr>
<tr>
<td><strong>IL-10-1082 rs1800896</strong></td>
<td>A/A</td>
<td>86 (86.0)</td>
<td>96 (90.6)</td>
<td>Additive</td>
</tr>
<tr>
<td></td>
<td>A/G</td>
<td>13 (13.0)</td>
<td>8 (7.7)</td>
<td>Dominant</td>
</tr>
<tr>
<td></td>
<td>G/G</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td>Recessive</td>
</tr>
<tr>
<td><strong>IL-10-1352 rs1800893</strong></td>
<td>G/G</td>
<td>86 (86.0)</td>
<td>96 (90.6)</td>
<td>Additive</td>
</tr>
<tr>
<td></td>
<td>G/A</td>
<td>13 (13.0)</td>
<td>9 (8.5)</td>
<td>Dominant</td>
</tr>
<tr>
<td></td>
<td>A/A</td>
<td>1 (1.0)</td>
<td>1 (0.9)</td>
<td>Recessive</td>
</tr>
</tbody>
</table>

*IL*, interleukin; SNP, single nucleotide polymorphism; FS, febrile seizure; FS+, febrile seizure plus; GEFS+, genetic epilepsy with febrile seizure plus.
significant negative association with FS, FS+, and GEFS+ compared to controls. Thus, this results may suggest that AA genotypes at TNF-α-863 show protective effects against FS, FS+, and GEFS+. However, our study population is small, so further study is needed with larger number of patients.

Pro-inflammatory cytokines play major actions in seizure generation and exacerbation [17]. IL-1β and TNF-α showed elevated levels in brains of experimental animals after electrical stimulation of the amygdala [18]. TNF-α is mostly released by microglia in the brain [19] and induces astrocytes to release glutamate [20]. An increase in extracellular glutamate may stimulate glutamatergic neurons, leading neuronal hyper-excitability. TNF-α upregulates α-amino-3-hydroxy-5-methyl-4-isoxazolepropanic acid (AMPA) receptors, increasing glutamatergic transmission [21]. TNF-α also upregulates endocytosis of gamma-Aminobutyric acid, or γ-aminobutyric acid (GABA) receptors, and eventually suppresses effects of the inhibition [22]. Altogether TNF-α leads to increase seizure susceptibility [22,23].

TNF-α is a potent pro-inflammatory cytokine showing implications with a large number of human diseases including many autoimmune diseases [7]. TNF-α shows alternate roles depending on variants of TNF-α gene regulating its effect and production [24]. Therefore, genetic variants that upregulate cytokine production may increase susceptibility to inflammation; subsequently, an exaggerated pro-inflammatory cytokine responses during infection may predispose in certain children to develop FS and subsequent epilepsy, especially FS+, and GEFS+. The postictal serum levels of IL-1β, IL-6, TNF-α, and high mobility group box 1 (HMGB1) showed significant elevation among children with FS attacks and children with epilepsy in afebrile seizure attacks, shown in our previous study [25].

<table>
<thead>
<tr>
<th>Gene variants</th>
<th>Allele</th>
<th>No. (%)</th>
<th>Allelic association P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-10-592 rs1800872</td>
<td>A</td>
<td>148 (74)</td>
<td>149 (70)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>52 (26)</td>
<td>63 (30)</td>
</tr>
<tr>
<td>IL-10-819 rs1800871</td>
<td>T</td>
<td>148 (74)</td>
<td>149 (70)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>52 (26)</td>
<td>63 (30)</td>
</tr>
<tr>
<td>IL-10-1082 rs1800896</td>
<td>A</td>
<td>185 (93)</td>
<td>198 (95)</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>15 (7)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>IL-10-1352 rs1800893</td>
<td>G</td>
<td>185 (93)</td>
<td>201 (95)</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>15 (7)</td>
<td>11 (5)</td>
</tr>
</tbody>
</table>

Table 4. Comparison of allelic frequencies of 4 IL-10 SNPs between the patients with FS, FS+, and GEFS+ versus controls

<table>
<thead>
<tr>
<th>Gene variants</th>
<th>Allele</th>
<th>No. (%)</th>
<th>Allelic association P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-10-592 rs1800872</td>
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<td>IL-10-819 rs1800871</td>
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<td>148 (74)</td>
<td>149 (70)</td>
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<td>C</td>
<td>52 (26)</td>
<td>63 (30)</td>
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<tr>
<td>IL-10-1082 rs1800896</td>
<td>A</td>
<td>185 (93)</td>
<td>198 (95)</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>15 (7)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>IL-10-1352 rs1800893</td>
<td>G</td>
<td>185 (93)</td>
<td>201 (95)</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>15 (7)</td>
<td>11 (5)</td>
</tr>
</tbody>
</table>

Table 5. Haplotype frequency analysis between FS, FS+, and GEFS+ versus controls

FS, febrile seizure; FS+, febrile seizure plus; GEFS+, genetic epilepsy with febrile seizure plus; TNF-α, tumor necrosis factor-α; IL, interleukin.
than AA genotype.

Korean Reference Genome DB KRGDB (http://coda.nih.go.kr/coda/KRGDB/index.jsp) are the free database of 1,100 Korean genomes. A allele frequency of TNF-a-863 is 15% and genotype frequencies are no available. In our study, A allele frequency is 15% in patients group of FS, FS+, and GEFS+ and 20% in controls; therefore, we can assume that our study population is not deviant to the general Korean population. The GG genotypes of TNF-a-238 were more prevalent than GA genotype among FS compared to controls in an Iranian study [9]. However, in our Korean population, there were no significant genotypic differences at TNF-a-238 in patient group of FS, FS+, and GEFS+ compared to controls.

TNF-a-308 is reported to have an association with higher susceptibility to asthma, atopic dermatitis, increased fatality in meningococcemia and ankylosing spondylitis [29-32]. However, in FS meta-analysis study, TNF-a-308 genotype showed no significant association [5-8]. Our study also showed no significant association at TNF-a-308 with FS, FS+, and GEFS+.

IL-10 is a major cytokine having anti-inflammatory action in immune system. IL-10 injected animals showed significantly higher threshold for provoking FS attacks than that in the controls, suggesting a protective effect to FS development [10]. IL-10 serum levels are controversial in several FS studies with some reporting increased [33] or others not increased levels [3,34].

IL-10 transmits negative feedback signals to decrease the immune system activation upon various inflammatory stimuli [35]. The IL-10-592, -819, and -1082 are placed in the IL-10 promoter regions having putative regulatory actions [36]. In a study of Japanese FS patients, the frequencies of the IL-10-592C/-819C/-1082A haplotype were significantly lower than controls [10]. In our study, the haplotype frequencies of IL-10-592C/-819C/-1082A/-1352G were also decreased in patient group with FS, FS+, and GEFS+ compared to controls, although statistically insignificant (18.5% vs. 24.5%, P = 0.497). In contrast, Iranian FS study reported that IL-10-592, -819, and -1082 showed no significant allelic association [11].

The limitation of our study is relatively small number of patients enrolled. Therefore, further studies with larger number of patients with different ethnicities are needed to reveal the exact association of TNF-a gene variants with FS, FS+, and GEFS+ in children.

In summary, allelic and genotypic frequencies of TNF-a and IL-10 promoter variants showed no significant differences between FS, FS+, and GEFS+ versus controls. However, AA genotypes at TNF-a-863 were present only in controls; therefore, TNF-a-863 (rs1800630) promoter variants may be negatively associated with FS, FS+, and GEFS+. Our results support that the promoter genetic variant linked to lesser production of pro-inflammatory cytokine TNF-a may be implicated in the protection to fever-provoked seizures in Korean children.

Conflicts of interest

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

Acknowledgements

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (No. 2016R1A2B4009438), the Seoul National University Hospital Research Fund (No. 03-2015-0120 and No. 04-2012-0140), and the Seoul National University Boramee Hospital Research Fund (No. 03-2011-15, No.03-2013-8 and No.01-2014-11) to Jieun Choi, and by grants from the NRF funded by the Korean government (MEST) (No. 2014R1A4A1008625 and 2017R1A2B3006704) to Jeon-Soo Shin.

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Jeon-Soo Shin, https://orcid.org/0000-0002-8294-3234

References

6. Chou IC, Lin WD, Wang CH, Tsai CH, Li TC, Tsai FJ. Interleukin (IL)-1beta, IL-1 receptor antagonist, IL-6, IL-8, IL-10, and


32. Nadel S, Newport MJ, Booy R, Levin M. Variation in the tumor ne-
crosis factor-alpha gene promoter region may be associated with
34. Virta M, Hurme M, Helminen M. Increased plasma levels of
pro- and anti-inflammatory cytokines in patients with febrile
35. Youn Y, Sung IK, Lee IG. The role of cytokines in seizures: in-
terleukin (IL)-1beta, IL-1Ra, IL-8, and IL-10. Korean J Pediatr
36. Eskdale J, Wordsworth P, Bowman S, Field M, Gallagher G. Asso-
ociation between polymorphisms at the human IL-10 locus and
Purpose: Acquired epileptic aphasia (AEA) accompanied by electroencephalogram (EEG) abnormality is a rare disease; therefore, there are few studies investigating the prognostic factors and treatment efficacy. We aimed to determine the therapeutic effects and prognostic factors for clinical seizure and neuropsychological function in acquired aphasia patients.

Methods: We retrospectively studied cases of AEA diagnosed at Severance Children’s Hospital from January 2013 to October 2017. We evaluated the efficacy of antiepileptic drugs, steroids, and ketogenic diets (KD) in treating acquired aphasia. The EEG patterns and prognostic factors were predicted by the background EEG and frequency of spike and wave during sleep (SWS).

Results: The study analyzed 20 patients, 11 male and 9 female, with AEA. Aphasia most likely occurred at 4 years of age, and clinical seizure was most likely to occur between 2 and 4 years of age and focal seizures were the most common seizure type. KD was shown to be the best treatment for clinical seizure in AEA patients. Patients with normal EEG background showed better responses to clinical seizure treatment and improvements in neuropsychological function.

Conclusion: KD and steroids generate the best therapeutic effects for clinical seizure in AEA patients. Improvements in neuropsychological function in AEA patients may be related to the EEG background and the SWS patterns. Additionally, the results suggest that the response of clinical seizure to antiepileptic drugs may also be related to the EEG background. However, the current study had some limitations and further research is needed.

Keywords: Aphasia; Landau-Kleffner syndrome; Epilepsy

Introduction

Acquired epileptic aphasia is a sudden or progressive language impairment with an abnormality in the electroencephalogram (EEG) [1-3]. Some researchers have reported that epileptiform EEG discharges can affect not only language impairment but also neurocognitive function [3,4]. Language impairment with an abnormality in the EEG is observed in some epilepsy syndrome, such as electrical status epilepticus during sleep (ESES), continuous spike and wave during slow sleep (CSWS), and Landau-Kleffner syndrome (LKS) [3]. In much of the previous literature, CSWS and ESES were used interchangeably and LKS considered a subtype of CSWS [2-5].

Acquired epileptic aphasia is commonly referred to as LKS, which was first introduced in 1957 [1]. It usually shows auditory agnosia with focal or multifocal spikes or spike and wave dis-
This study was approved by the Institutional Review Board (IRB) of Yonsei University (IRB no., 4-2016-0080). Informed consent was waived due to the retrospective nature of the study.

Results

In our patient cohort, 11 patients (55%) were males and nine patients (45%) were females. Aphasia occurred at 2 to 9 years of age, with six patients (30%) occurring at the age of 4, three patients (15%) at the age of 3, and three patients (15%) at the age of 7. Most commonly, clinical seizure in acquired aphasia occurred at 2, 3, and 4 years of age. Their clinical seizures were focal motor seizures (12 patients, 60%), generalized motor seizures (six patients, 30%), and dyscognitive type seizures (two patients, 10%).

When the EEG background wave was analyzed, seven patients (35%) showed a normal background rhythm, whereas 11 patients (55%) showed a GSW background pattern. The most common EEG patterns during sleep were focal CSWS patterns ≥ 85%, which occurred in 10 patients (50%), and generalized CSWS patterns ≥ 85%, which occurred in six patients (20%).

The most effective treatment for seizure in acquired aphasia was KD, followed by steroid administration, with 100% and 90% treatment efficacy, respectively. We also analyzed the relationship between EEG background pattern and treatment efficacy. VPA was used in a total of 18 patients and showed a positive effect in 10 of these 18 patients (56%). In patients with GSW EEG background activity, five of 10 patients (50%) were effectively treated with VPA, and in patients with normal EEG background activity, five of six patients (83.3%) were effectively treated with VPA. LEV was used in 11 patients, of which seven patients were effectively treated by the drug. In patients with normal background EEG, LEV was effective at treating all three patients it was prescribed to. In patients with GSW EEG background, LEV was effective in treating four of six patients. Ten patients who did not respond to AEDs were treated with steroids, nine patients (90%) showed a response to treatment. Ten patients who had a recurrence after steroid therapy and did not respond to AEDs were treated with KD, 10 patients (100%) showed a response to treatment. Steroids were used in patients with normal EEG background (n = 4), GSW (n = 5), and FSW (n = 1). In the case of GSW background rhythm, all five patients were effectively treated for the clinical seizure. Similarly, the one patient with FSW was also effectively handled for the clinical seizure by steroid administration. KD was used in patients with normal (n = 3), disorganized (n = 1), and GSW (n = 6) EEG backgrounds, and was effective in treating all patients (Table 1). In the comparison of treatment effect on seizure and the frequency of SWS, VPA was

Materials and Methods

We retrospectively analyzed 20 patients (11 males, nine females) with acquired aphasia diagnosed at Severance Children’s Hospital from January 2013 to October 2017. Patients with acquired aphasia were included in the study, with or without seizures. They were assessed via EEG for more than 4 hours, and this test was examined by the International 10 to 20 system. EEG background waves were divided into four patterns: normal, disorganized, generalized slowing (GSW), and focal slowing (FSW). The frequency of spike and wave during sleep (SWS) on the EEG was grouped according to frequency as ≥ 85% and 50% to 84%, and divided into generalized and focal types according to the pattern. The response to different treatments was analyzed using the antiepileptic drugs (AEDs), valproate (VPA), and levetiracetam (LEV), in addition to other treatments, namely steroid and ketogenic diets (KDs). Treatment effects were assessed by clinical seizure at each outpatient clinic. We consider a positive effect of treatment that the frequency of seizures was reduced by 50% or more, and continued these statuses for more than 6 months. If it did not meet the above criteria, the treatment option was added or changed. The evaluation of neuropsychological function was evaluated through evaluation tools such as Korean Wechsler Intelligence Scale for Children. The test was performed at the time of diagnosis and 3 to 6 months later, and the results were evaluated by comparing the two tests.

Patients were enrolled in the study if they showed language impairment irrespective of the type of clinical seizure, including cases with no specific findings on their brain magnetic resonance imaging.

We excluded epileptic encephalopathy such as Lennox-Gastaut syndrome, which may accompany other cognitive impairments.

charges on the EEG which are continuous or nearly continuous during sleep [5].

CSWS shows general developmental difficulties including linguistic problems, and more than 85% of continuous spikes and waves in the EEG are seen during sleep. Usually, these are seen as bilateral and symmetric, but it could be shown asymmetric or focal patterns [6-12]. CSWS shows premorbid central nervous system dysfunction whereas LKS rarely indicates such [5].

Acquired aphasia with clinical seizures is a rare disease, and the prognostic factor of treatment and the cognitive outcome were less studied. In this study, we investigated the prognosis of neuropsychological function and therapeutic effect of clinical seizures through EEG in patients who have a language impairment with clinical seizure without distinguishing between LKS and CSWS.

Materials and Methods

We retrospectively analyzed 20 patients (11 males, nine females) with acquired aphasia diagnosed at Severance Children’s Hospital from January 2013 to October 2017. Patients with acquired aphasia were included in the study, with or without seizures. They were assessed via EEG for more than 4 hours, and this test was examined by the International 10 to 20 system. EEG background waves were divided into four patterns: normal, disorganized, generalized slowing (GSW), and focal slowing (FSW). The frequency of spike and wave during sleep (SWS) on the EEG was grouped according to frequency as ≥ 85% and 50% to 84%, and divided into generalized and focal types according to the pattern. The response to different treatments was analyzed using the antiepileptic drugs (AEDs), valproate (VPA), and levetiracetam (LEV), in addition to other treatments, namely steroid and ketogenic diets (KDs). Treatment effects were assessed by clinical seizure at each outpatient clinic. We consider a positive effect of treatment that the frequency of seizures was reduced by 50% or more, and continued these statuses for more than 6 months. If it did not meet the above criteria, the treatment option was added or changed. The evaluation of neuropsychological function was evaluated through evaluation tools such as Korean Wechsler Intelligence Scale for Children. The test was performed at the time of diagnosis and 3 to 6 months later, and the results were evaluated by comparing the two tests.

Patients were enrolled in the study if they showed language impairment irrespective of the type of clinical seizure, including cases with no specific findings on their brain magnetic resonance imaging.

We excluded epileptic encephalopathy such as Lennox-Gastaut syndrome, which may accompany other cognitive impairments.
an effective treatment in five of 10 patients (50%) with ≥ 85% focal SWS, whereas LEV was effective in one of three patients (33.3%) with ≥ 85% focal SWS. Steroids were an effective treatment for five of six patients (83.3%) and KD was effective in five of five patients (100%) with ≥ 85% focal SWS. In the case of ≥ 85% of generalized SWS, VPA was effective in four of six patients (66.7%), LEV was effective in three of five patients (60%), and both steroid and KD were effective in four of four patients (100%). The above contents are summarized in Table 1.

We compared neuropsychological function with EEG background activity and the frequency of SWS in acquired aphasia. Ten patients had normal neuropsychological function and 10 patients had delayed function. In patients with normal neuropsychological function, six patients (60%) showed normal EEG background and four patients (40%) showed GSW EEG background. In patients with normal EEG background, six patients (85.7%) showed normal neuropsychological function and one patient (14.3%) showed delayed function. EEG background activity showed a GSW pattern in seven patients (70%) with delayed neuropsychological function. We also analyzed the correlation between pattern and frequency of SWS and neuropsychological function. There were 14 patients with focal abnormalities who included SWS ≥ 85% pattern and six patients with generalized SWS ≥ 85% on EEG. Seven patients (50%) with focal abnormality on EEG showed mild to moderate neuropsychological abnormality and seven patients (50%) with focal abnormality were normal neuropsychological function and three patients (50%) with generalized SWS ≥ 85% were normal cognitive function. However, one patient (17%) generalized SWS ≥ 85% on EEG showed severe neuropsychological abnormality (Fig. 1). This is the only patient with severe cognitive impairment in this study. In 10 patients with abnormal neuropsychological function, the functional improvement was seen in nine cases with non-generalized background rhythm or focal epileptiform discharges in EEG but neither GSW of EEG background nor generalized CSWS patients showed functional improvement (Table 2).

**Discussion**

Our results show similar onset age of clinical symptoms to that reported by the existing literature [13]. In this study, the most common age of aphasia onset was 4 years, and the period of clinical seizure was most commonly 2 to 4 years of age. In our study, most patients with aphasia showed ≥ 85% CSWS, more commonly exhibiting focal CSWS patterns than the generalized

![Fig. 1](https://doi.org/10.26815/acn.2019.00059)

**Table 1.** The effect of treatment for clinical seizure on EEG patterns

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal (n = 7)</th>
<th>DO (n = 1)</th>
<th>GSW (n = 11)</th>
<th>FSW (n = 1)</th>
<th>Total</th>
<th>Focal CSWS ≥ 85% (n = 10)</th>
<th>Focal CSWS 50%–84% (n = 2)</th>
<th>Generalized CSWS ≥ 85% (n = 6)</th>
<th>Focal abnormality (n = 2)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA</td>
<td>5/6 (83.3)</td>
<td>0/1 (0)</td>
<td>5/10 (50)</td>
<td>0/1 (0)</td>
<td>10/18 (56)</td>
<td>5/10 (50)</td>
<td>0/1 (0)</td>
<td>1/1 (100)</td>
<td>4/6 (66.7)</td>
<td>0/1 (0)</td>
</tr>
<tr>
<td>LEV</td>
<td>5/6 (83.3)</td>
<td>0/1 (0)</td>
<td>4/6 (66.7)</td>
<td>0/1 (0)</td>
<td>7/11 (64)</td>
<td>1/3 (33.3)</td>
<td>2/2 (100)</td>
<td>3/5 (60)</td>
<td>1/1 (100)</td>
<td>7/11 (63.6)</td>
</tr>
<tr>
<td>Steroid</td>
<td>3/4 (75)</td>
<td>-</td>
<td>5/5 (100)</td>
<td>1/1 (100)</td>
<td>9/10 (90)</td>
<td>5/6 (83.3)</td>
<td>-</td>
<td>4/4 (100)</td>
<td>-</td>
<td>9/10 (90)</td>
</tr>
<tr>
<td>KD</td>
<td>3/3 (100)</td>
<td>1/1 (100)</td>
<td>6/6 (100)</td>
<td>-</td>
<td>10/10 (100)</td>
<td>5/5 (100)</td>
<td>-</td>
<td>4/4 (100)</td>
<td>1/1 (100)</td>
<td>10/10 (100)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

EEG, electroencephalogram; CSWS, continuous spike and wave during sleep; DO, disorganized; GSW, generalized slowing; FSW, focal slowing; VPA, valproate; LEV, levetiracetam; KD, ketogenic diet.
CSWS pattern. The correlation between EEG background activity and treatment for clinical seizure was difficult to find. However, when patients with ≥ 85% focal CSWS and patients with ≥ 85% generalized CSWS were compared, it was found that overall the latter responded well to treatment. Among the treatments considered, steroid administration and KD was found to be most effective, consistent with previous studies [14-16]. The results also show, using two different AEDs, VPA and LEV, that patients with normal EEG background activity show greater treatment response, and those AEDs were more effective in patients with generalized CSWS patterns than focal patterns. The efficacy for clinical seizure patients with CSWS > 85% on EEG and the generalized pattern seems to be better. However, the therapeutic effect of LEV for clinical seizure showed a better effect in less than 84% CSWS and simple focal abnormality of EEG epileptiform pattern. So, we propose keeping in mind the epileptiform pattern of EEG when treating clinical seizures with acquired aphasia.

At diagnosis, 50% of patients showed normal neuropsychological function, while 45% showed mild to moderate delayed function. Among the patients with normal neurological function, 60% showed normal EEG background, whereas 70% of patients with delayed neurological function showed GSW EEG background. Therefore, the results suggest that EEG background activity is related to neuropsychological function in patients with CSWS. Among the patients with delayed function, one patient showed no improvement following treatment. In the relationship between prognosis of neuropsychological function and EEG, we found that the generalized pattern on EEG got a poor outcome than other patterns and the patients with focal CSWS patterns were usually mildly delayed, whereas those with generalized CSWS patterns were severely delayed. Through these results, we could consider that the generalized pattern in the EEG affects cognitive function and would suggest that the EEG background pattern may help predict the prognosis of neuropsychological function.

We could consider that the EEG pattern will be helpful in the treatment of clinical seizure and prediction for neuropsychological prognosis in acquired aphasia. However, this study has a limitation due to a small number of patients identified in a single center. Additional studies will be needed in the future to elucidate this relationship further.

Conflicts of interest

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

Acknowledgements

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant number: HI18C0586).

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References


Reconsideration of Vigabatrin Effect in Infantile Spasms Treatment

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**Purpose:** To investigate the effect of vigabatrin (VGB) as a therapeutic agent for patients with infantile spasms (IS), compare risk factors for treatment response, and review safety of VGB by assessing its side effects.

**Methods:** Among 35 patients admitted to the Department of Pediatric Neurology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea who received initial monotherapy with VGB under diagnosis of IS, 23 patients who met our inclusion criteria were enrolled and their medical records were retrospectively reviewed.

**Results:** Of these 23 patients, average age at diagnosis was 7.26 ± 4.8 months and average age at spasms was 6.20 ± 3.8 months. Average treatment lag was 1.09 ± 1.8 months. Thirteen patients (56.5%) achieved seizure free status. There was no ophthalmic complication among patients. Remission of hypsarrhythmia at 3 and 6 months after treatment was a good prognostic factor (P=0.026 and P=0.004, respectively).

**Conclusion:** VGB is effective enough to become a first-line drug for children with IS. Better prognosis can be expected in patients with clinical remission of hypsarrhythmia on electroencephalography after treatment initiation using VGB compared to those who do not have such remission. Regular eye examination and follow-up check-up are also needed in parallel with the use of VGB.

**Keywords:** Spasms, infantile; Vigabatrin

**Introduction**

Infantile spasms (IS) are intractable epilepsies classified as epileptic encephalopathy in the International League Against Epilepsy (ILAE) [1]. They typically present three clinical features: epileptic spasms, developmental delay, and the presence of hypsarrhythmia on electroencephalography (EEG) under 2 years old [2]. They do not respond well to conventional anticonvulsant. Thus, adrenocorticotropic hormone (ACTH), steroid, and vigabatrin (VGB) have been used as initial therapeutic agents [3].

VGB was first marketed for treating intractable complex partial seizure and IS in the United Kingdom (UK) in 1989. VGB is an irreversible, selective inhibitor of enzyme-activated gamma aminobutyric acid transaminase. It suppresses gamma aminobutyric acid transaminase catabolism and enhances the activation of interneurons by increasing availability of gamma aminobutyric acid in synaptic cleft [4]. In addition, VGB can partially inhibit mammalian target of rapamycin and glial proliferation in animal model of tuberous sclerosis complex [5]. However, some studies have shown increased risk of peripheral visual field defects.
(VFDs) by VGB in adults and children [6]. Thus, the use of
VGB has been limited for a while. The frequency of VFDs has
been reported to be 21% to 34% in Western studies [7-9]. Tau-
rine deficiency [10,11] and reversible magnetic resonance imaging (MRI) changes [12,13] might play considerable roles in the
development of VFDs. Nevertheless, it is inadequate to conclude
that all ethnicities in the world will develop VFDs after using
VGB as there have been no collected baseline data of patients
prior to VGB administration. In 2009, the United States Food
and Drug Administration approved the use of VGB as a mono-
therapy in 1 month old to 2 years old children with IS since
VFDs seemed to be related to prolonged administration of VGB
and accumulated quantity of VGB in the body [14]. In 2013,
VGB was also approved as a therapeutic agent for older patients
(> 10 years old) with intractable complex partial seizures.

The use of ACTH for patients with IS is impossible in South
Korea at present time. Therefore, there are very limited options
for patients with IS in our country. Recently, it has been reported
that the incidence of VFDs is not significantly increased when
VGB is used for a short period of time [15-17]. Therefore, we
need to reconsider the use of VGB as a therapeutic agent for pa-
tients with intractable epilepsy including IS. Thus, the objective
of this study was to investigate the effect of VGB in patients with
IS and identify factors closely related to the treatment by com-
paring two groups (treatment responder group and treatment
non-responder group). In addition, the safety of VGB was re-
viewed by assessing its side effects.

Materials and Methods

1. Study subjects
Among 35 patients admitted to the Department of Pediatric
Neurology, Seoul St. Mary’s Hospital, College of Medicine, The
Catholic University of Korea from April 2009 to June 2018 who
received initial monotherapy with VGB under the diagnosis of
IS, 23 patients (13 males, 10 females) aged 2 months old to 2
years old who had follow-up check-up for 6 months or more
were enrolled. Exclusion criteria were: (1) any symptom or EEG
interpretation inappropriate for diagnosis of IS, (2) initial thera-
py using agents other than VGB, and (3) patients who failed to
make follow-up check-up for 6 months or more.

All participants were referred to the Department of Ophthal-
mology for eye examination prior to treatment and at 3 and 6
months after initiation of treatment. There was a limitation for
visual field examination due to patient’s age. Thus, visual adverse
effects were identified through visual evoked potential (VEP),
funduscopic examination, and guardian’s questionnaire.

This was a retrospective study with data collected from medi-
cal records of participants. This study was approved by the Insti-
tutional Review Board (IRB) of Seoul St. Mary’s Hospital, Col-
lege of Medicine, The Catholic University of Korea (IRB num-
ber: KC17RESI0535). Written informed consent by the patients
was waived due to a retrospective nature of our study.

2. Methods
IS was diagnosed based on clinical features and EEG findings
of patients. The feature of epileptic spasm is a brief, bilateral sym-
metrical contraction of muscles involving neck, body, and extre-
mities. In addition, there must be a presence of hypsarrhyth-
mia or modified hypsarrhythmia on EEG. Based on onset age of
seizures, participants were divided into four groups: 6, 6 to 12, 12
to 18, and 18 to 24 months.

Potential risk factors such as age of onset, age at diagnosis, sex,
birth history, presence of developmental delay, brain MRI find-
ings, treatment lag (delayed period between clinical onset of
spasms and initiation of treatment), presence of hypsarrhythmia
on EEG, and clinical remission of hypsarrhythmia after the treat-
ment were used to examine their associations with VGB treat-
ment response. Participants were divided into two groups ac-
cording to outcome of treatment. Each potential risk factor was
statistically analyzed by comparing the two groups. All patients
underwent Bayley scales of Infant Development-II test to assess
developmental delay. Patients who showed 25% or more delay in
one developmental area were defined as having developmental
delays.

Initial dose of VGB was 40 to 50 mg/kg/day administered in
two divided doses. The dose of VGB was gradually increased ev-
ery 2 days to a target dose of 100 mg/kg/day. However, if the pa-
tient responded to a given lower dose of medication, the dose
was maintained without further increase. When a patient did not
respond to a dose of 100 mg/kg/day, the patient was treated with
polytherapy in combination with other treatments such as ste-
roid pulse therapy without increasing VGB dose.

The effect of VGB treatment on participants were evaluated at
6 months after the treatment based on decrease in frequency of
spasms as a clinical evaluation criterion. Participants were divid-
ed into three groups based on the decrease in frequency of
spasms: group 1, completely resolved; group 2, resolved more
than 50%; and group 3, resolved less than 50%. For statistical
analysis, patients in groups 2 and 3 were assigned to treatment
non-responder group. IBM SPSS version 24.0 (IBM Co., Ar-
monk, NY, USA) was used for all statistical analyses. To distin-
guish the difference between treatment responder group and
treatment non-responder group, independent t-test was used.
when normality assumption was available whereas Mann-Whitney U test was used when the normality assumption was unavailable. Chi-square test was used to determine the relationship with independent variables. Result was considered statistically significant when P value was less than 0.05.

**Results**

From April 2009 to June 2018, 35 patients who were admitted to the Department of Pediatric Neurology, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, received initial monotherapy with VGB under the diagnosis of IS. Only 23 patients (males 13, females 10) met the study criteria. Data of each patient including sex, birth history, developmental delay, brain MRI findings are shown in Table 1.

Of these 23 patients, their average age at spasms was 6.20 ± 3.8 months. Among age groups, those who were less than 6 months old accounted for the most (60.9%, 14 patients). Average age at diagnosis of IS was 7.26 ± 4.8 months. Twenty patients (86.9%) were diagnosed with IS before 12 months of age and 13 patients were diagnosed before the age of 6 months old. Treatment lag time ranged from less than 1 to 9 months, with average treatment lag of 1.09 ± 1.8 months.

Birth complications were reported in eight patients (34.8%), Table 1.

### Table 1. Demographic features of cohort, comparison of responders and non-responders

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cohort (n = 23)</th>
<th>Responders (n = 13)</th>
<th>Non-responders (n = 10)</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of spasms (mo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6</td>
<td>6.20 ± 3.8 (1–15)</td>
<td>4.89 ± 2.6 (1–8)</td>
<td>7.90 ± 4.5 (2.5–13)</td>
<td>0.056</td>
</tr>
<tr>
<td>6&lt;n≤12</td>
<td>14 (60.9)</td>
<td>9 (69.2)</td>
<td>5 (50.0)</td>
<td></td>
</tr>
<tr>
<td>12&lt;n≤18</td>
<td>3 (13.0)</td>
<td>0</td>
<td>3 (30.0)</td>
<td></td>
</tr>
<tr>
<td>18&lt;n≤24</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (mo)</td>
<td>7.26 ± 4.8 (2–22)</td>
<td>5.61 ± 2.5 (2–9)</td>
<td>9.40 ± 6.2 (3–22)</td>
<td>0.058</td>
</tr>
<tr>
<td>≤ 6</td>
<td>3 (56.5)</td>
<td>8 (61.5)</td>
<td>5 (50.0)</td>
<td></td>
</tr>
<tr>
<td>6&lt;n≤12</td>
<td>7 (30.4)</td>
<td>5 (38.5)</td>
<td>2 (20.0)</td>
<td></td>
</tr>
<tr>
<td>12&lt;n≤18</td>
<td>2 (8.7)</td>
<td>0</td>
<td>2 (20.0)</td>
<td></td>
</tr>
<tr>
<td>18&lt;n≤24</td>
<td>1 (4.3)</td>
<td>0</td>
<td>1 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Treatment lag (mo)</td>
<td>1.09 ± 1.8 (0–9)</td>
<td>0.77 ± 0.6 (0–2)</td>
<td>1.50 ± 2.7 (0–9)</td>
<td>0.974</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.580</td>
</tr>
<tr>
<td>Male</td>
<td>13 (56.5)</td>
<td>8 (61.5)</td>
<td>5 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10 (43.5)</td>
<td>5 (38.5)</td>
<td>5 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Birth history</td>
<td></td>
<td></td>
<td></td>
<td>0.179</td>
</tr>
<tr>
<td>Non-specific</td>
<td>15 (65.2)</td>
<td>10 (66.7)</td>
<td>5 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>8 (34.8)</td>
<td>3 (37.5)</td>
<td>5 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Brain magnetic resonance imaging</td>
<td></td>
<td></td>
<td></td>
<td>0.103</td>
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<tr>
<td>Non-specific</td>
<td>7 (30.4)</td>
<td>6 (46.2)</td>
<td>1 (10.0)</td>
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</tr>
<tr>
<td>Abnormal</td>
<td>16 (69.6)</td>
<td>7 (53.8)</td>
<td>9 (90.0)</td>
<td></td>
</tr>
<tr>
<td>Developmental delay</td>
<td></td>
<td></td>
<td></td>
<td>0.161</td>
</tr>
<tr>
<td>Yes</td>
<td>20 (87.0)</td>
<td>10 (76.9)</td>
<td>10 (100)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3 (13.0)</td>
<td>3 (23.1)</td>
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<td></td>
</tr>
<tr>
<td>Hypsarrhythmia at 1 mo after treatment</td>
<td></td>
<td></td>
<td></td>
<td>0.673</td>
</tr>
<tr>
<td>Resolving</td>
<td>8 (34.8)</td>
<td>5 (38.5)</td>
<td>3 (30.0)</td>
<td></td>
</tr>
<tr>
<td>Remain</td>
<td>15 (65.2)</td>
<td>8 (61.5)</td>
<td>7 (70.0)</td>
<td></td>
</tr>
<tr>
<td>Hypsarrhythmia at 3 mo after treatment</td>
<td></td>
<td></td>
<td></td>
<td>0.026</td>
</tr>
<tr>
<td>Resolving</td>
<td>15 (65.2)</td>
<td>11 (84.6)</td>
<td>4 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Remain</td>
<td>8 (34.8)</td>
<td>2 (15.4)</td>
<td>6 (60.0)</td>
<td></td>
</tr>
<tr>
<td>Hypsarrhythmia at 6 mo after treatment</td>
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<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>Resolving</td>
<td>18 (78.3)</td>
<td>13 (100)</td>
<td>5 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Remain</td>
<td>5 (21.7)</td>
<td>0</td>
<td>5 (50.0)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean±SD (range) or number (%).

*a*Calculated by chi-square test, independent t-test and Mann-Whitney U test.
including five cases (62.5%) of prematurity, four cases (50%) of hypoxic-ischemic encephalopathy, three cases (12.5%) of intraventricular hemorrhage, and one case (12.5%) of subgaleal hemorrhage. In addition, 20 of 23 patients (87.0%) had developmental delay. Abnormal brain MRI findings were shown in 16 patients (69.6%). The most common abnormal findings were hypoxic ischemic encephalopathy (five cases) and periventricular leukomalacia (three cases).

Response of patients to VGB treatment was evaluated based on frequency of spasms. Number of patients in groups 1 (completely resolved), 2 (resolved more than 50%), and 3 (resolved less than 50%) were 13 (56.5%), six (26.1%), and four (17.4%), respectively. There was no difference in dose of VGB between the groups. No patient showed significant side effects to discontinue the drug. All patients had normal ophthalmologic findings.

Clinical remission of hypsarrhythmia on EEG was also checked. One month after using VGB, the pattern of hypsarrhythmia was resolved in eight patients (34.8%). After 3 months of treatment with VGB, 15 patients (65.2%) showed clinical remission of hypsarrhythmia. After 6 months of VGB treatment, five of 23 patients (21.7%) still had hypsarrhythmia.

Analysis of age distribution at diagnosis showed that the average age at diagnosis in the treatment responder group (5.61 ± 2.5 months) was younger than that in the treatment non-responder group (9.40 ± 6.2 months). Onset age of seizures was also younger in the treatment responder group (4.89 ± 2.6 months) than that in treatment non-responder group (7.90 ± 4.5 months). All patients in the treatment responder group started treatment for seizure before 12 months of age. However, neither age at diagnosis nor onset age showed statistically significant association with treatment response (P = 0.058 and P = 0.056).

Average treatment lag was 0.77 ± 0.6 months in the treatment responder group (13 patients) and 1.50 ± 2.7 months in the treatment non-responder group (10 patients). Although treatment lag was longer in the treatment non-responder group than that in the treatment responder group, the difference between the two was not statistically significant (P = 0.056).

In the treatment responder group (13 patients), three patients (37.5%) presented with abnormal birth history. In the treatment non-responder group (10 patients), five patients (50%) had remarkable birth history. Although birth history was more remarkable in the treatment non-responder group, the difference was not statistically significant (P = 0.179). Seven patients (53.9%) in the treatment responder group and nine patients (90.0%) in the treatment non-responder group had abnormal brain MRI findings. Ten of 13 patients (76.9%) in the treatment responder groups and 10 patients (100%) in the treatment non-responder group had developmental delay. However, neither brain MRI findings nor developmental delay showed statistically significant differences between the two groups (P = 0.103 and P = 0.161, respectively).

Regarding clinical remission of hypsarrhythmia, at 1 month after treatment, 61.5% (eight patients) in the treatment response group and 70% (seven patients) in the treatment non-responder group still presented with hypsarrhythmia, showing no significant difference between the two groups (P = 0.673). At 3 months after treatment, 84.6% (11 patients) in the treatment responder group appeared to have clinical remission of hypsarrhythmia whereas 40% (four patients) in the treatment non-responder group presented clinical remission of hypsarrhythmia on EEG, showing statistically significant difference between the two groups (P = 0.026). EEG test performed at 6 months after the initiation of treatment revealed that all patients (100%) in the treatment responder group and 50% patients in the treatment non-responder group had clinical remission on hypsarrhythmia, showing statistically significant difference between the two groups (P = 0.004).

Discussion

ACTH, steroid, and VGB are considered as drugs of choice for IS. However, ACTH is currently unavailable in South Korea while high dose of steroid is known to cause various side effects on endocrine system of patients. On the other hand, VGB is an initial therapy that is effective and relatively safe in children with IS. Previous studies have reported that about 35% to 80% of patients become seizure free after treating with VGB [18-20]. In our study, 56.5% of patients achieved seizure free when they used VGB as initial monotherapy, showing effects comparable to those of past researches.

There are various potential risk factors for IS, including sex, history of neonatal seizures, age of onset, abnormal brain MRI findings, treatment lag, and accessibility to medical institution for treatment [18,21,22]. The present study revealed that patients with clinical remission of hypsarrhythmia after 3 months from the initiation of treatment with VGB had better treatment response overall, supporting many articles showing that hypsarrhythmia was an important prognostic factor [22-25]. At 1 month after initiation of treatment with VGB, hypsarrhythmia was only resolved in 34.8% of patients. There was no statistically significant treatment response. However, EEG test performed at 3 months after the initiation of treatment with VGB revealed that 65% to 79% of patients showed clinical remission of hypsarrhythmia and achieved seizure free, consistent with existing researches.
Therefore, regular evaluation is important to determine patient’s outcome even if hypsarrhythmia persists in EEG test. Many animal studies and retrospective studies have discussed bilateral VFDs due to use of VGB [6,10-14]. However, no patient in the present study experienced such adverse drug reaction when regular eye examination was performed, consistent with a small prospective study recently conducted in Japan [16]. In addition, a recent study has reported that VFDs are caused by the disease itself rather than the use of VGB [17]. However, that study had limitations such as small sample size, short duration of study period, and lack of patient’s cooperation for eye examination that might have resulted in inaccuracy of eye examination. Hence, different methods such as VEP, funduscopic examination, and electroretinography need to be used to compensate the limitation of eye examination on children. Regular follow-up check-up is necessary even after completing treatment with VGB.

In conclusion, VGB is effective enough to become a first-line drug for children with IS. Better prognosis can be expected for patients with clinical remission of hypsarrhythmia on EEG after treatment initiation using VGB. Regular eye examination and follow-up check-up are also needed in parallel with the use of VGB. Since this is a retrospective study by analyzing medical records of a small number of patients, large-scale studies are needed in the future.

Conflicts of interest

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

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References


Acute and chronic headaches are common in children. Most headaches can be classified as primary headaches. About 27% of girls and 20% of boys complain of frequent or severe headaches [1]. Chronic headache can be defined when the headache persists for more than 3 months and is accompanied by headache for more than 15 days per month. The probability of chronic headache in children is known to be 2% to 4% in female children and 0.8% to 2% in male children. However, a chronic headache can be excluded from the class of chronic headaches in the case of an underlying disease or structural abnormality [2]. Headaches from structural causes are very rare in children [1]. Nasal polyps are benign polypoidal masses arising mainly from chronic inflammation and edema of the mucous membranes in the nose and paranasal sinuses [3]. The presenting symptoms of nasal polyps include nasal obstruction, rhinorrhea, postnasal drip, anosmia, and headache. Symptoms can vary depending on the site and size of the polyps, but a severe headache is a rare symptom in children [4]. This paper reports a case of antrochoanal polyp with a severe headache in child.

The patient, an 8-year-old girl, complained of a headache that had been present for approximately 3 months. Symptoms worsened one month ago, and there the analgesic did not have an effect. The headache was usually a dull pain on the whole area of the head, with the greatest pain on the left parietal region, and each episode lasted for about 4 hours. There was no aura, and symptoms were aggravated by walking or moving the temporomandibular joints when eating. The symptoms were relieved when the patient was lying down and resting. The patient did not experience discomfort due to symptoms such as nasal obstruction or rhinorrhea, but she could not consume any food due to the pain. The patient reported having previously been healthy and had no history of allergy. Her family history was nonspecific. At the time of admission, the patient’s blood pressure was 110/66 mm Hg, and there were no abnormal findings from the physical examination. We obtained brain magnetic resonance image (MRI) for a severe headache, which revealed sinusitis in the left ethmoidal, and both sphenoidal and right maxillary sinus and nasal polyp in the left sphenoethmoidal recess (Fig. 1A and B).

We consulted the department of otorhinolaryngology and executed paranasal sinus computed tomography, which revealed an antrochoanal polyp in the left sphenoethmoidal recess with sphenoid sinus widening, and associated sinusitis in the left ethmoidal and sphenoidal sinuses (Fig. 1C and D). The patient was taken to the endoscopic sinus surgery for the removal of polyp, and the endoscopic examination yielded...
After surgery operation, the patient progressed very well and experienced complete relief of her severe headache without any additional medication including analgesic and antibiotic therapy. She remained asymptomatic and disease-free, at the 4-month follow-up.

Nasal polyps can be seen in 0.2% to 1% of the total population, of which antrochoanal polyps account for 33% of children. The most common nasal polyp is cystic fibrosis. However, cystic fibrosis is mainly observed in children younger than age 12. Antrochoanal polyp is the most common type of choanal polyp, and the most common symptom is obstruction of the nasal passage. Symptoms such as rhinorrhea, epistaxis, and allergy-related symptoms may also be present. As in our case, polyp can cause obstructive sleep symptoms, proptosis, and diplopia. Headaches can be seen in 15.7% of children and 37.5% in adults [4]. How-

Fig. 1. Brain magnetic resonance image showed (A, B) sinusitis in the left ethmoid, sphenoid, right maxillary sinus, and nasal polyp in the left sphenoidomoidal recess (white arrows) and (C, D) Paranasal sinus computed tomography showed antrochoanal polyp in the left sphenoidomoidal recess with sphenoid sinus widening (black arrows), and associated sinusitis in the left ethmoid and sphenoid sinuses.

Fig. 2. Left nasal cavity endoscopic view showed antrochoanal polyp (white arrow).
ever, it is not easy to distinguish between headaches attributed to polyps or chronic headaches. A report on the relationship between chronic daily headaches and quality of life (QOL), shows that QOL decreases as the use of analgesics increases. It is known that the progression to chronic headache rather than the intensity of pain affects QOL more. It is also known that 25.4% of chronic headache patient have experienced drug overdose [5]. Therefore, it is necessary to provide proper evaluation and management for secondary headaches. In the case of antrochoanal polyp, such as those which our patient had, surgery can be the primary treatment [3]. However, these surgical approaches require long-term prognosis study and follow-up because of the risk of developing teeth, bone growth and facial hyperesthesia, but the research involving children is still limited [4]. In our case, the patient, who was consistently medicated but no improvement of signs, did not complain of a headache after endoscopic polyp removal. Therefore, after surgical treatment, headache improved rapidly, and the origin of headache attributed to disorder of the nasal septum, mucosa, and infection could be excluded.

On histopathology, allergic polyps are more common in children than are inflammatory polyps. Therefore, medical treatment such as oral and topical nasal steroid administration may necessary if allergy polyps are present [4]. However, as in our case, the headache was completely relieved without common symptoms, such as nasal obstruction and rhinorrhea even though there was no additional antibiotic therapy.

In summary, this case presents a child patient with antrochoanal polyp and severe headache symptoms. She was diagnosed based on clinical features and brain MRI. The surgery completely relieved her severe headache.

Conflicts of interest

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

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References

Rotavirus infection–associated posterior reversible encephalopathy syndrome

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Rotavirus is an important cause of severe gastroenteritis in infants and children. Generally, rotavirus infections are self-limiting benign diseases but occasionally can cause a wide range of neurological manifestations, including benign febrile or afebrile convulsions, meningoencephalitis, cerebellitis, and lethal encephalitis or encephalopathy [1]. However, it is unclear how rotavirus can affect the central nervous system without direct invasion.

Posterior reversible encephalopathy syndrome (PRES) is a well-recognized clinical disorder with typical neuroimaging findings consisting of mostly transient bilateral gray and white matter abnormalities in the posterior cerebral hemispheric regions and cerebellum [2]. The common clinical symptoms are headache, confusion, seizures, and visual disturbances such as cortical blindness. These symptoms usually recover without sequelae following appropriate treatment. Common precipitants are sudden elevations of blood pressure, renal failure, fluid restriction, and treatment with immunosuppressive drugs such as cyclosporine [3]. Recently, studies related to infection-associated PRES have been published [2,4]. We describe the case of a 6-year-old boy with rotavirus gastroenteritis who developed clinical and radiological manifestations consistent with PRES.

A previously healthy 6-year-old boy was referred to the pediatric emergency room with a 4-day history of vomiting and abdominal pain despite being treated with fluid therapy at a private clinic. His development was normal, and his past medical history was unremarkable. On examination, the patient was conscious, mildly dehydrated, and afebrile. At the time of admission, his blood pressure was 110/70 mm Hg (normal range, 97 to 115/57 to 76) and heart rate was 90 beats/minute (normal range, 75 to 118). The boy experienced sudden visual and consciousness disturbances on the day of hospital admission for fluid treatment. A few hours later, he had a generalized tonic convulsion for 3 minutes without definite fever. The results of a routine blood test at that time showed no abnormalities except for mildly elevated inflammatory markers: white blood cell count, 16.3 × 10^3/μL; hemoglobin, 14.9 g/dL; platelet count, 426 × 10^3/μL; total CO₂, 26.7 mmol/L; sodium, 134 mEq/L; potassium, 3.7 mEq/L; chloride, 98 mEq/L; C-reactive protein, 1.40 mg/dL; glucose, 151 mg/dL; ammonia, 26 μmol/L; and calcium ionized, 1.23 mmol/L. His blood pressure increased slightly to 133/85 mm Hg but remained relatively stable.

We announced this report as a poster presentation in 43th meeting of Korean Child Neurology Society, 2017.
demonstrated bilateral multifocal patchy (more prominent in the left) increased fluid attenuated inversion recovery (FLAIR) signal intensity (negative on diffusion-weighted MRI) at both occipito-parietal cortices, and some nearby white matter areas exhibited slight obliteration (Fig. 1). Rotavirus antigen was detected in a stool specimen by latex agglutination. Parents remembered that their child had not been vaccinated with rotavirus and this was the spring of the epidemic of rotavirus infection. Electroencephalography showed semirhythmic high amplitude 1.5 to 2 Hz delta activities on both occipital areas (Fig. 2).

We immediately administered intravenous methylprednisolone (30 mg/kg/day for 3 days) and continued conservative treatments. MRI taken 12 hours later showed interval resolution of previously noted vasogenic edema, gyral swelling, and decreased FLAIR signal intensity (Fig. 1). His clinical condition improved over the next 2 days. Visual evoked potential testing revealed a delay of evoked potential latencies in the left eye. He was discharged on hospital day 10 without any neurologic complications. Two weeks later, follow-up brain MRI showed that the previous lesions were disappeared (Fig. 1).

In this case, rotavirus gastroenteritis developed in a patient who was older than most patients with rotavirus. Convulsive symptoms related to rotavirus infection may occur as PRES without definite fluctuation of blood pressures. Approximately one-third of patients with PRES have normal or only mildly increased blood pressure, though most are hypertensive [4,5]. PRES is an increasingly recognized disorder readily diagnosed via brain MRI in clinical practice. There is a wide clinical spectrum of both symptoms and triggers, and yet it remains incompletely understood. The most widely accepted theory is that severe hypertension interrupts brain autoregulation [5]. In patients with impaired cerebral autoregulation, uncontrolled hypertension leads to hyperperfu-

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**Fig. 1.** Brain magnetic resonance imaging (A, B) axial fluid attenuated inversion recovery (FLAIR) obtained 12 hours after the onset of symptoms showing bilateral multifocal patchy hyperintensity at the both parietooccipital, left high frontal cortex, and some nearby white matter areas. Axial FLAIR (C) obtained 24 hours after the onset of symptoms showing interval resolving previous vasogenic edema, gyral swelling, and hyperintensened lesions, and axial T2-weighted imaging (D) revealed normal finding. After 2 weeks, axial FLAIR (E) and T2-weighted imaging (F) showed interval normalized, disappeared previous lesions.  

https://doi.org/10.26815/acn.2019.00101
and cerebral vessel damage, which can cause fluid to leak into the brain parenchyma, eliciting vasogenic edema [5]. However, as mentioned earlier, a significant proportion of patients do not demonstrate hypertension. An alternative theory is that systemic inflammation causes endothelial dysfunction [4]. In a systemic inflammatory process such as sepsis, eclampsia, transplantation, and autoimmune disease, the vasoconstriction that occurs during autoregulation could exacerbate pre-existing inflammatory endothelial dysfunction, causing hypoxia and subsequent vasogenic edema [5]. We can explain why a typical PRES without hypertension developed in this case of infection-associated PRES. However, we are not sure whether age affected the patient’s symptoms. There have been only two cases reported so far: parainfluenza virus infection in an adult and rotavirus infection in an infant [4,5]. In other words, infection-associated PRES, as well as hypertension-associated PRES, contribute endothelial dysfunction to the pathophysiology of this clinical-radiological syndrome.

In summary, this case describes a patient with rotavirus infection-associated PRES with a good prognosis. Pediatricians should be well aware that rotavirus gastroenteritis-induced convulsions have a wide spectrum and may be related to reversible posterior leukoencephalopathy. Prompt diagnosis and treatment, including stopping precipitating factors when possible, are crucial to achieving good reversibility.

**Conflicts of interest**

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

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**References**

Instructions to authors

General information

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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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The materials and study design should be presented in detail. In experimental research, methods should be described in such a manner that the experiments can be reproduced by the readers. The sources of special chemicals or preparations should be given (name of company, city and state, and country). Clinical studies or experiments using laboratory animals or pathogens should include approval of the studies by relevant committees. A statement concerning IRB approval and consent procedures must be presented.

Clearly describe the selection of observational or experimental participants (healthy individuals or patients, including controls), including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age, sex, or ethnicity is not always known at the time of study design, researchers should aim for inclusion of representative populations into all study types and at a minimum provide descriptive data for these and other relevant demographic variables.

Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.

Results
This section should include a concise textual description of the data presented in the tables and figures. Excessive repetition of table or figure contents should be avoided.

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Acknowledgment
The acknowledgments section should contain brief statements of assistance and financial support. Any other matters associated with research funds, facilities and drugs that were used in the study should also be given.

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   3) Titles of tables should be concise using a phrase or a clause. The first character should be capitalized.
   4) Tables should be concise and not duplicate information found in figures.
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