Aims and scope
Annals of Child Neurology is an interdisciplinary peer-reviewed biomedical journal publishing articles in the fields of child neurology, pediatric neururosurgery, pediatric neuroradiology, child psychiatry, pediatric neuropsychology, developmental and behavior pediatrics, pediatric neuroscience, 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, neuropsychiatric, neuromaging, neuromuscular medicine, neuromicrobiology 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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Editorial

1 Celebrating 1st Birthday: Reborn into Eternity
   Soonhak Kwon

Review articles

2 Benign Convulsions with Mild Gastroenteritis
   Young Ok Kim

8 Febrile Infection-Related Epilepsy Syndrome: Refractory Status Epilepticus and Management Strategies
   Yun-Jin Lee

Original articles

16 Clinical Differences between Enterovirus and Human Parechovirus in Children and Infants
   Seonkyeong Rhie

23 Semiological Features of Nonepileptic Paroxysmal Events in Infancy
   Ha Rim Noh, Young Hwan Kim, Kye Hyang Lee

30 The Efficacy and Safety of Rituximab for the Treatment of Pediatric Autoimmune Neuroinflammatory Disorders at a Single Center
   Young Jun Ko, Young Kyu Shim, Woo Joong Kim, Soo Yeon Kim, Hunmin Kim, Hee Hwang, Jong-Hee Chae, Ji Eun Choi, Ki Joong Kim, Byung Chan Lim

Letters to the editor

37 Oroolingual Tremor on Smiling
   Sun Ah Choi, Jeesuk Yu, Hee Hwang, Hunmin Kim

39 Guillain-Barré Syndrome Presenting with Unilateral Peripheral Facial Palsy in an Infant
   Ha Rim Noh, Kye Hyang Lee
We are very delighted to celebrate the first anniversary of *Annals of Child Neurology* with you, our readers. I personally consider 2019 as the year of creative destruction for us. It was the year that we made a tremendous change in the scope of the journal, from the *Journal of the Korean Child Neurology Society* rooted since 1993 into an international, open access journal called *Annals of Child Neurology*. Despite the overwhelming worry *Annals of Child Neurology* has experienced a fairly long, but successful journey over the past year. We have published four issues and 25 articles covering a wide range of topics, such as epilepsy, genetic, infectious, inflammatory, and other neurological conditions. We made it!

I would like to express my sincere thanks to the distinguished members of our editorial board and our colleagues who serve as reviewers for their hard work. The members of our editorial board have given their priceless time to advise us to step forward. Our reviewers provided timely, objective and scientific evaluation necessary to accept or reject papers for publication. They have been able to choose the most valuable manuscripts based on the quality and the significance of study. Thanks are also due to the staff at M2 community and InfoLumi for their superb support. Without their dedication, *Annals of Child Neurology* simply could not survive. I am positive that *Annals of Child Neurology* will gradually get over the potential weakness by setting up a few fundamental frameworks such as a proficiently functioning scheme for processing manuscripts, a prestigious editorial board and reviewers with cool heads but warm hearts. *Annals of Child Neurology* will make new ways to ‘never-thought-before’ world in near future and the reader will find it practical and useful.

As always, we welcome and encourage constructive feedback and commentaries. Lastly, we hope you will celebrate with us at *Annals of Child Neurology* and visit us frequently at our web site, www.annchildneurol.org.

Best wishes and thank you in advance for your contribution to *Annals of Child Neurology*.

**Conflicts of interest**

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

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Benign convulsions with mild gastroenteritis (CwG) are a well-known type of benign seizures that occur in infants and children aged between 6 months and 3 years and are associated with acute (viral) gastroenteritis. The pathogens found in the stool of CwG patients are mostly rotavirus or norovirus, which can result in mild dehydration. Short-lasting seizures (≤5 minutes) occur in clusters within 24 hours, without provoking features such as fever, abnormal laboratory findings in the blood (e.g., hypoglycemia, hyponatremia, or hypocalcemia), or abnormal results in the cerebrospinal fluid (e.g., central nervous system infection). Electroencephalography in CwG patients shows normal or mildly abnormal findings, and brain imaging findings are normal. Affected children develop normally before and after the seizures. The occurrence of seizures does not require the repeated use of first- or second-line intravenous antiepileptic drugs in the acute stage or daily antiepileptic drug medications, since they usually do not recur and have a good prognosis. Patients with CwG rarely have a family history of epilepsy. Although the mean interval between enteric symptom onset and seizure onset in CwG is roughly 2 days, some patients can experience seizures before enteric symptoms, meaning that clinicians should exercise caution during early winter and spring, when the prevalence of CwG is especially high. Additionally, reports of CwG in Korea are roughly as common as in Japan and other East Asian countries, and pediatricians should therefore be familiar with its clinical characteristics and take care not to overprescribe antiepileptic drugs in patients with CwG.

Keywords: Seizures; Gastroenteritis; Norovirus; Rotavirus; Infant

Introduction

Seizures in infancy and early childhood are frequently a major problem for the families of patients, especially if they are not simple febrile seizures with a good prognosis. If an infant younger than 6 months developed normally before the onset of the first seizure and experiences short-lasting afebrile seizures occurring once or twice a day, a clinician can first consider benign infantile seizures [1]. However, when the patient has symptoms of diarrhea and/or vomiting before or after seizures, this can indicate the presence of benign convulsions with mild gastroenteritis (CwG) [2-31]. Additionally, if the season is early winter or spring when rotavirus and norovirus are prevalent, CwG have to be considered in patients especially between 13 to 24 months of age with short-lasting seizures (less than 5 minutes) occurring in clusters [3-12,15,16,19,24].

CwG are benign convulsions that occur between the ages of 6 months and 3 years, with this age range first defined by Komori et al. [3] in 1995. However, the age range of patients with CwG has been estimated in the literature as being as broad as from 1 month to 6 years [2-20,22-26,30,31]. Hypoglycemia, an electrolyte imbal-
ance such as hyponatremia or hypocalcemia, and central nervous system infection that can trigger seizures have to be excluded in this definition [2-31]. The acute gastroenteritis in these benign convulsions is mostly caused by rotavirus or norovirus [2-11,14-20,22-26]. Since CwG have been reported as frequently in Korea as in Japan, pediatricians need a good knowledge of their clinical characteristics and treatment [4-7,28,29].

Definition

The Japanese clinician Morooka [2] first reported patients with CwG in 1982. There were few reports of CwG in East Asian countries around Japan until the early 2000s [2,3,9-11], but it has been widely detected even in Western countries since the mid-2000s [12,17,19,20]. Following the first report by Morooka [2], Komori et al. [3] summarized the characteristics of CwG and tried to define this condition in 1995. Although there is still no categorized and constant definition, CwG can be easily recognized based on previously reported concepts: (1) benign seizures in children typically aged between 6 months and 3 years (or maximally between 1 month and 6 years); (2) normal development before and after seizures; (3) afebrile seizures with acute (viral) gastroenteritis that usually occur in winter and can cause mild dehydration, with the pathogens mostly being rotavirus or norovirus; (4) short-lasting recurrent seizures occurring within 24 hours (maximally within a few days); (5) neither laboratory abnormalities such as hypoglycemia and electrolyte imbalance nor abnormal findings in cerebrospinal fluid; (6) normal or mildly abnormal findings in electroencephalography (EEG); (7) normal findings in brain imaging; and (8) seizures having a good prognosis [2-31]. Relatively few patients with CwG have a family history of epilepsy [3,10,24-26,30].

Pathogens

The infectious pathogens of gastroenteritis found in patients with CwG are rotavirus, norovirus, adenovirus, astrovirus, and sapovirus [3-11,14-20,22-26]. Rotavirus is the most frequently reported, occurring in 40% to 50% patients with CwG before the rotavirus vaccine was introduced [3,5,10,15,17,23,24]. Rotavirus vaccines were introduced in South Korea in 2007, with the vaccination rate reaching 50% in 2009 [32,33]. These vaccines have decreased the rate of rotavirus positivity in patients with CwG, but the total incidence of CwG did not decrease since the incidence of norovirus infections has increased to become the leading pathogen in recent years [4-6]. Two Korean single-center studies performed after 2012 revealed 63.0% to 67.5% positivity for norovirus in patients with CwG [4,6]. The descriptions of the clinical characteristics have differed somewhat between rotaviral and noroviral CwG in a few studies; however, these had some limitations due to the small numbers of patients compared and the different prevalence periods of the two pathogens [4,5,15]. Afebrile seizures occur more frequently in patients with noroviral gastroenteritis than in those with rotaviral gastroenteritis, according to studies performed in Taiwan (29.7% vs. 5%) and Hong Kong (8.67% vs. 1.29%) [16,21]. The pathophysiologic mechanisms underlying seizures in patients with CwG are still unclear. The following two questions remain unanswered [7,8]: (1) are seizures in CwG caused by the direct invasion of viruses into the central nervous system or are they an indirect effect of viruses on the brain with circulating mediates such as cytokines, and (2) why are only infants and young children susceptible to CwG? Rotavirus mainly replicating in the gastrointestinal tracts has been detected in blood, which suggests possibility of the viral spread to the brain [34-39]. Rotavirus nonstructural protein 4 (NSP4) that is an important glycosylated protein for viral pathogenicity has been detected in rotavirus-infected neurons [36]. NSP4 has been mentioned as a major enterotoxin causing neurotoxicity by direct viral invasion or cytokine dysregulation [7,8,37]. Recently, Yeom et al. [37] detected that serum levels of anti-NSP4 immunoglobulin G (IgG) antibodies were lower in the seizure group with rotaviral gastroenteritis than those in the non-seizure group, which suggested the protective effect of anti-NSP4 IgG against seizures. The pathogenesis of norovirus and other viruses resulting in CwG has been still not-well understood [7,8,40]. Therefore, common hypothesis explaining pathogenic mechanism in CwG has not been proposed yet.

Rotavirus has been reported in more severe neurologic diseases than CwG: encephalopathy (e.g., mild encephalopathy with a reversible splenial lesion [MERS]), meningoencephalitis and cerebellitis [7,8,38,39]. Norovirus also has been detected in patients with encephalitis/encephalopathy [40]. A recent nationwide survey in Japan from 2011 to March 2016 showed how poor the outcome of norovirus-associated encephalitis/encephalopathy (NoVE) was in children [40]. NoVE in this survey included MERS, acute necrotizing encephalopathy, acute encephalopathy with biphasic seizures and late reduced diffusion, and hemorrhagic shock and encephalopathy [40].

Epidemiology

The incidence of CwG peaked at an age of 13 to 24 months regardless of the types of viruses involved (Fig. 1) [3-20,22-26]. The study of Kawano et al. [15] from 2007 found that nine patients with noroviral CwG were younger than 30 patients with ro-
taviral CwG. However, recent studies have found no age difference between noroviral CwG patients and rotaviral CwG patients (Table 1) [4,6]. A nonsignificant sex difference has been found in patients with CwG, with females constituting 55% to 60% of them [4,6,7,11,15]. A female predominance seemed more likely in patients with noroviral CwG (61.4% to 68.9%) than those with rotaviral CwG (50.0% to 53.5%) [4,6,15].

The most-common season for CwG is winter, independent of the virus type [3-12,15,16,18,19,24]. However, rotaviral CwG were most prevalent from January to May in East Asian countries (from winter to spring), while noroviral CwG were most prevalent during November and December (only in winter) (Fig. 2) [4,15,24].

Clinical characteristics

CwG occur in distinctive clusters, which were noted in 57% to 75% of patients and reportedly involved a maximum of eight episodes in each cluster [3,5,7,10,15,17,24,30]. In the study of Kim et al.,

![Fig. 1. Age at onset of convulsions with mild gastroenteritis [4,5].](image1)

![Fig. 2. Monthly distribution of convulsions with mild gastroenteritis [4,5].](image2)

Table 1. Clinical characteristics of patients with convulsions with mild gastroenteritis at a single center between March 2005 and February 2017 [4,5]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Norovirus</th>
<th>Rotavirus</th>
<th>Total</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>44</td>
<td>26</td>
<td>140</td>
<td>0.68</td>
</tr>
<tr>
<td>Age (mo)</td>
<td>18.66±5.57</td>
<td>19.31±7.37</td>
<td>18.45±6.22</td>
<td>0.68</td>
</tr>
<tr>
<td>Female sex</td>
<td>27 (61.4)</td>
<td>13 (50.0)</td>
<td>77 (55.0)</td>
<td>0.36</td>
</tr>
<tr>
<td>Enteric symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present at seizure onset</td>
<td>44 (100.0)</td>
<td>26 (100.0)</td>
<td>140 (100.0)</td>
<td>0.25</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34 (77.3)</td>
<td>23 (88.5)</td>
<td>116 (82.9)</td>
<td>0.02c</td>
</tr>
<tr>
<td>Vomiting</td>
<td>43 (97.7)</td>
<td>21 (80.8)</td>
<td>120 (85.7)</td>
<td>0.04c</td>
</tr>
<tr>
<td>Interval (day)b</td>
<td>2.00±1.06</td>
<td>2.58±1.21</td>
<td>2.11±1.14</td>
<td>0.04c</td>
</tr>
<tr>
<td>Number of seizures</td>
<td>2.73±1.37</td>
<td>2.15±1.16</td>
<td>2.41±1.35</td>
<td>0.08</td>
</tr>
<tr>
<td>1</td>
<td>9 (20.5)</td>
<td>11 (42.3)</td>
<td>44 (31.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>2</td>
<td>12 (27.3)</td>
<td>4 (15.4)</td>
<td>34 (24.3)</td>
<td>0.26</td>
</tr>
<tr>
<td>3</td>
<td>11 (25.0)</td>
<td>7 (26.9)</td>
<td>39 (27.9)</td>
<td>0.86</td>
</tr>
<tr>
<td>4</td>
<td>8 (18.2)</td>
<td>4 (15.4)</td>
<td>12 (9.3)</td>
<td>0.77</td>
</tr>
<tr>
<td>≥5</td>
<td>4 (9.1)</td>
<td>0</td>
<td>10 (7.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>Seizure duration (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>42 (95.5)</td>
<td>24 (92.3)</td>
<td>129 (92.1)</td>
<td>0.58</td>
</tr>
<tr>
<td>&gt;5–15</td>
<td>2 (4.5)</td>
<td>2 (7.7)</td>
<td>9 (6.4)</td>
<td>0.58</td>
</tr>
<tr>
<td>&gt;15</td>
<td>0</td>
<td>0</td>
<td>2 (1.4)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

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

*P value for comparison between rotavirus- and norovirus-associated convulsions with mild gastroenteritis; bInterval between enteric symptom onset and seizure onset; cP<0.05.
al. [4], multiple seizures occurred in 79.5% of the noroviral patients but 57.7% of the rotaviral patients (P = 0.05) (Table 1). The number of seizures was 2.41 ± 1.35 for the 140 CwG patients in this study: 2.73 ± 1.37 in the noroviral group (44 patients) and 2.15 ± 1.16 in the rotaviral group (26 patients; P = 0.08) (Table 1) [4]. Another Korean study of noroviral CwG similarly found that the number of seizures was 2.79 ± 2.82 [6].

One seizure episode lasts mostly for shorter than 5 minutes, although a few episodes last 15 minutes (Table 1) [4,10,15]. All seizure episodes from the first to the last mostly occur within 24 hours [4,10,15]: Kim et al’s [4] recent study found that 62.1% of seizure episodes stopped within 6 hours, 87.1% within 12 hours, and 96.4% within 24 hours (Fig. 3). Although Kawano et al. [15] reported that all episodes of clustered seizures stopped earlier in rotaviral patients than in noroviral patients group (4.9 ± 5.7 hours vs. 11.8 ± 12.0 hours), this result was not replicated in Kim et al’s [4] study.

The interval between enteric symptom onset and seizure onset in CwG was 2.11 ± 1.14 days according to Kim et al’s [4] study that included 140 CwG patients (Table 1). This interval was 2.00 ± 1.06 days in 44 noroviral CwG patients but 2.58 ± 1.21 days in 26 rotaviral CwG patients (P = 0.04) (Table 1), although Kawano et al. [15] found no significant difference between the two groups. A recent study from 2016 similarly found that this interval in noroviral CwG was 1.82 ± 0.78 days [6]. Some patients can experience seizures before enteric symptoms, although most CwG patients had seizures after enteric symptoms (Table 1) [3-5], and so clinicians should exercise caution during the prevalent season of CwG. Vomiting was more common in norovirus-associated CwG patients (97.7%) than in rotavirus-associated CwG patients (80.8%) in Kim et al’s [4] previous study, although vomiting was usually less frequent in noroviral gastroenteritis than in rotaviral gastroenteritis (Table 1) [16]. This needs further investigation.

Seizure semiology of CwG has been differently described in the literature [3,4,6,17]. In two recent Korean studies, generalized onset seizures were seen in more than 90% of CwG patients irrespective of the virus type [4,6]. However, focal onset seizures were not less common than generalized onset ones in the studies of Komori et al. [3] (52.6%; 10 of 19 seizures in 10 CwG patients) and Cara-balbo et al. [17] (68.5%; 15 of 22 CwG patients). In fact, seizures in most ictal EEG recordings were focal onset ones [19,24].

The interictal EEG recordings in CwG are mostly normal, although they can show posterior slowing or focal sharp/spikes [3-8,10-12,15-20,24-26]. Kim et al’s [4] previous study found that posterior slowing was more frequent in norovirus patients (34.9%) than in rotavirus patients (11.5%), while another Korean study of noroviral CwG observed focal or diffuse slowing in only 13.8% patients [4,6]. The findings of brain imaging were all normal in Kim et al’s [4] previous study as well as in most other previous studies [4-8,15-20,24-26].

Most laboratory profiles in patients with CwG are within the normal ranges, but there are some reports of serum uric acid levels being high, including Kim et al’s [4] recent report (9.53 ± 0.48 mg/dL in 26 CwG patients) [4,27-29]. Yoo et al. [29] identified that serum uric acid levels in 154 patients with CwG were significantly higher (9.79 ± 2.16 mg/dL) than in 3092 patients with acute gastroenteritis without seizures (6.04 ± 2.36 mg/dL). Additionally, they showed that the serum levels of uric acid in CwG patients are not confounded by dehydration or recurrent seizures that have been considered as the underlying patho-mechanisms of high uric acid levels [29]. Yoo et al. [29] suggested that significantly-high serum uric acid levels can be a valuable diagnostic clue for CwG, although further basic studies to reveal its mechanism are in need. Comparisons of laboratory profiles between rotaviral and noroviral CwG patients in the literature have shown different results, which therefore need to be evaluated further with larger numbers of patients [4,15]. Although Kawano et al. [15] revealed no significant difference, Kim et al’s [4] recent study showed a slight difference, with a higher platelet count (318,090 ± 88,920/mm³ vs. 263,080 ± 97,070/mm³, P = 0.02), lower serum glucose level (76.86 ± 14.96 mg/dL vs. 86.58 ± 18.65 mg/dL, P = 0.02), and higher serum calcium level (9.65 ± 0.59 mg/dL vs. 9.41 ± 0.37 mg/dL, P = 0.04) in the patients with noroviral CwG than in those with rotaviral CwG.

Treating CwG in the acute stage when seizures develop in clusters does not require repeated injections of first- and second-line antiepileptic drugs, as seizures in CwG patients are characteristically short-lasting (≤ 5 minutes/episode) and all episodes of clus-

Fig. 3. Interval from the first to the last seizure [4,5].
tered seizures usually stop within 24 hours from seizure onset [10,14,15,23]. According to Japanese colleagues’ reports, benzodi-
azepines are not so effective, while carbamazepine (orally 5 mg/kg once daily for 1 to 3 days) and lidocaine have been effective in some patients with recurrent seizures [10,14,15,23]. Additionally, no daily antiepileptic drug medication is required since the seizures usually do not recur [10,14,15,23].

The prognosis of CwG is good, with the affected children developing normally before and after seizures and having no disability even when experiencing clustered seizures during the acute stage [2,7,30,31]. Progression to epilepsy from CwG has been rarely reported [7,8,22,24].

Conclusion

CwG are afebrile, nonprovoked, and archetypal seizures that occur during infancy and early childhood and have a good prognosis, and are associated with acute viral gastroenteritis and no abnormal findings in brain imaging. The most common pathogen was rotavirus before the rotavirus vaccine was introduced around 2010, and has been norovirus since then, with both of these viruses being most prevalent during winter. Short-lasting and clustered seizures occur within 24 hours, but they need neither repeated use of first- and second-line intravenous antiepileptic drugs in the acute stage nor daily antiepileptic drug medication. EEG in CwG patients shows normal or only mildly abnormal findings. The children develop normally before and after seizures and most of them have no specific family history of seizures. Although most seizures develop within 2 days after the onset of enteric symptoms, pediatricians should exercise caution during the prevalent season of CwG since seizures can also precede the enteric symptoms.

Conflicts of interest

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

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Conceptualization: YOK. Data curation: YOK. Formal analysis: YOK. Project administration: YOK. Visualization: YOK. Writing-original draft: YOK. Writing-review & editing: YOK.

References


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Febrile infection-related epilepsy syndrome (FIRES) is a rare, catastrophic epileptic syndrome that strikes previously healthy children. Its pathogenesis is unknown, it has few treatments, and it is typically refractory. In FIRES, refractory status epilepticus or a cluster of seizures starts a few days after the onset of an acute febrile illness, and it may continue as drug-resistant epilepsy, with neuropsychological impairments occurring without latency. Clinical knowledge and guidelines on FIRES are limited because it is sporadic and extremely rare. To date, the absence of specific biomarkers poses a significant diagnostic challenge; nevertheless, early diagnosis is very important for optimal management. Despite treatment with multiple immunotherapies and anti-seizure medications, the majority of patients with FIRES are left with significant cognitive disabilities and refractory epilepsy. This review aims to highlight the most recent insights into the clinical features, terminology, epidemiology, pathogenesis, diagnostic challenges, and therapeutic options associated with FIRES.

Keywords: Seizures, febrile; Drug resistant epilepsy; Epileptic syndromes; Status epilepticus

Introduction

The acronym febrile infection-related epilepsy syndrome (FIRES) was first used by van Baalen et al. [1] in 2010, although the same clinical entity has been given different names by other authors [2]. If infectious encephalitis has been excluded, FIRES should be suspected whenever a previously healthy child presents with the explosive onset of severe status epilepticus (SE) refractory to even anesthetics, shortly after a brief, often convalescing, febrile illness [1]. The term refers to a rare disastrous epileptic encephalopathy with a yet undefined etiology, characterized by acute manifestation of recurrent seizures or refractory SE preceding febrile illness, but without evidence of infectious encephalitis.

In general, the etiology of FIRES is unclear, and alternative hypotheses of epileptogenesis exist. Despite the absence of biomarkers, early diagnosis is very important for optimal management as diagnostic and therapeutic delays contribute to poor outcomes following SE. In up to 60% of cases of de novo refractory SE, diagnostic work-up fails to identify the underlying etiology, which is the typical and problematic clinical situation associated with FIRES [3]. Because FIRES is extremely rare, this sudden and severe epileptic encephalopathy is challenging to clinicians. This clinical review focuses on correctly recognizing and managing FIRES.

Terminology

A number of names and acronyms have been proposed to describe the syndromes here referred to as FIRES, including new-onset re-
fractory status epilepticus (NORSE), acute encephalitis with refractory repetitive partial seizures (AERRPS), and devastating epileptic encephalopathy in school-aged children (DESC) [4]. Although described in adults, the clinical manifestations, course, and outcomes of NORSE are very similar to FIRES. Initially, NORSE was considered to be specific to the adult population while FIRES was specific of the pediatric population; however, current scientific evidence does not support differentiating the two syndromes [5]. The recently proposed consensus definition identifies FIRES as a subcategory of NORSE [5]. The consensus is that NORSE describes a clinical presentation, but is not a specific diagnosis, in a patient without active epilepsy or other existing relevant neurological disorder who experiences a new-onset of refractory SE in the absence of a clear acute or active structural, metabolic, or toxic cause. FIRES, as a subtype of NORSE requires a prior febrile infection, with fever starting between 24 hours and two weeks prior to the onset of refractory SE. Fever may or may not be present at the onset of SE, and patients may be of any age. This definition excludes prolonged febrile seizures, which usually occur in children who have had a new-onset of fever < 24 hours prior to the onset of seizures, or whose fever is recognized only after onset of seizures [6].

Epidemiology

Before the term FIRES was accepted, cases of encephalitis-related refractory SE caused by an unknown or assumed immune etiology were described using many different terms; therefore, it is difficult to extract epidemiological data from available literature. Based on a prospective hospital-based surveillance program conducted in Germany, van Baalen et al. [1] estimated the annual incidence and prevalence of FIRES among children and adolescents in Germany to be, 1:1,000,000 and 1:100,000, respectively. Although FIRES also occurs in adults, affected patients are mainly children between 5 and 13 years of age, with cases peaking during school age (between 4 and 9 years) and exhibiting male preponderance [4]. The outcomes associated with FIRES are poor, with a mortality rate of up to 30%, refractory epilepsy following the acute phase, and cognitive delay in 66% to 100% of the survivors [4]. Survivors with previously normal cognition typically develop learning disabilities, and only a minority survive the episode without any neurologic sequelae [4].

Etiology and pathophysiology

The pathogenesis of FIRES is still a matter of debate, with many diverse pathogenic cascades and mechanisms hypothesized. Metabolic, microbiologic, genetic, and immune analyses have not provided a clear mechanism. Mutations in genes associated with fever-sensitive epilepsy, such as sodium voltage-gated channel alpha subunit 1 (SCN1A), DNA polymerase subunit gamma (POLG1), and protocadherin-19 (PCDH19), or in genes associated with infection-triggered encephalopathy and SE are typically absent [5]. Several authors explored the possibility of FIRES being a form of severe infectious encephalitis [4]. However, no published data from brain biopsies of FIRES patients have produced typical findings of encephalitis [1]. It is possible that FIRES is caused by an inflammatory or autoimmune mechanism.

While analysis of cerebrospinal fluid (CSF) from FIRES patients often shows mild pleocytosis, evidence for an infection or a specific autoimmune condition is lacking. Nevertheless, high levels of proinflammatory cytokines/chemokines have been observed in the serum and CSF of patients with FIRES, indicating a role for the immune system in pathogenesis [7]. Sakuma et al. [8] reported a comprehensive study of the inflammatory mediators in children with AERRPS, and observed a detectable upregulation in proinflammatory cytokines/chemokines in the CSF. Changes in cytokines/chemokines levels were more prominent in the CSF than in the serum, suggesting that the inflammation primarily occurs in the central nervous system (CNS). Inflammation seems to contribute to the FIRES cascade through a generalized and ongoing lowering of the seizure threshold [9]. The slow, progressive nature of such a process may explain the delay in FIRES onset following a febrile illness. Progressive accumulation of inflammatory cytokines could then give way to a vicious cycle of aberrant hyperexcitability and/or a structural epileptogenic remodeling of brain networks [10]. Additionally, intrinsic factors, such as a genetic predisposition, may be responsible for the lack of an efficient resolution of the epileptogenic process [11].

The biphasic clinical course associated with FIRES is suggestive of an autoimmune mechanism triggered by an infection. In a few cases, CSF specimens from affected patients show lymphocytic pleocytosis and oligoclonal bands. Patient improvement with immune therapy supports the role of the immune system in the pathophysiology of FIRES [12]. However, the search for specific autoantibodies has so far yielded unconvincing results [2,4].

In conclusion, the underlying pathogenic mechanism of FIRES is likely to be a two-hit process, involving the synergistic effect between an immune response to a febrile illness or infection affecting the brain and an intrinsic predisposition toward an auto-sustaining epileptogenic process. The illustration for possible mechanisms of epileptogenesis in FIRES is shown in Fig. 1 [13].
Clinical manifestations

FIRES in previously healthy children generally has three phases. The first phase is the unremarkable febrile illness. The second phase follows between 24 hours and 2 weeks later, with acute, highly recurrent seizures, rapidly evolving into refractory SE. There may or may not be fever at the time of seizure. In approximately 50% of cases, no fever is observed at the time the seizure occurs [14]. Seizures may be focal or multifocal at onset, ranging from dozens to hundreds per day [4,15]. Seizure onset typically presents as a focal seizure, focal seizures with secondary generalization, or secondarily generalized seizures only [4]. Consciousness is impaired during the seizures. Autonomic symptoms, such as pallor, apnea, and cyanosis, have been noted in some patients [15]. SE typically lasts for 1 to 12 weeks, with an average of 3 weeks in duration [16]. The third and chronic phase of FIRES is a drug-resistant epilepsy with neuropsychological and cognitive impairment, occurring without latency as SE decreases [1]. Cluster seizures may occur every 2 to 4 weeks.

Diagnosis

As there is currently no known cause of FIRES, no specific test is available to confirm the diagnosis. Diagnosis depends on clinical assessment ruling out alternative infectious, alternative toxic, metabolic, and genetic etiologies in children with refractory SE in temporal proximity to a febrile illness. By definition, FIRES is a fever-triggered NORSE in patients free from preceding epilepsy or other neurological disorders and without clear or active causes [3]. Therefore, the initial clinical evaluation is crucial and an extensive work-up is necessary to exclude similar conditions associated with acute-onset of SE (Table 1). Careful history-taking, neurological examination, and routine laboratory testing may alternatively identify the most common etiologies of SE, such as discontinuation or changes in antiepileptic drugs (AEDs), intoxication, CNS infections, recent traumatic brain injury, or acute metabolic imbalances. CSF testing in patients with FIRES is usually negative, with mild or no pleocytosis, an absence of markers for viral infections or autoimmunity (oligoclonal band), and an absence of antineural antibodies (anti-voltage-gated potassium channel [VGKC] complex, anti-N-methyl-D-aspartate [NMDA] receptor, and anti-alpha-aminono-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] receptor) [17,18].

During the acute phase, standard electroencephalography (EEG) and continuous EEG monitoring are of supreme importance in guiding precise therapeutic interventions, assessing sedation levels, and recognizing nonconvulsive SE [19]. Clinically seizure semiology may indicate focal onset, and EEG ictal recordings
can confirm that discharges are often temporal or perisylvian with opercular extension. Interestingly, in a series of published studies, ictal and interictal EEG recordings showed a single epileptic focus in less than 10% of patients [18]. The frequent presence of a shifting focal ictal pattern indicates that both hemispheres are affected while interictal EEG findings show generalized slow waves [17]. Farias-Moeller et al. [20] described the three common features of acute EEG studies in seven patients with FIRES: gradual increase in seizure burden with evolution to SE, recurrent beta-delta complexes resembling extreme delta brush, and a characteristic electrographic seizure pattern, typically beginning with prolonged focal fast activity, followed by well-formed rhythmic spike-and-wave complexes. Unfortunately, EEG has limited value in differentiating FIRES from epilepsy or encephalopathy of autoimmune etiology.

Brain magnetic resonance imaging (MRI) is required to exclude structural abnormalities associated with refractory SE. Initial MRI scans may be negative, or may show abnormalities, predominantly in the temporal regions, insula, or basal ganglia, that may be either transient or irreversible [1,21]. Early MRI scans (within the first weeks) may show swelling in the mesial temporal structures, with increased signal on T2-weighted scans, as observed in autoimmune or limbic encephalitis [1,17]. Follow-up MRI scans (after 6 months) may show bilateral mesial temporal atrophy and increased T2-weighted signal in approximately 50% of cases [17]. Global changes may also occur. Focal abnormal signal changes over the periventricular white matter suggest that more extensive lesions are associated with a poorer clinical outcome [22].

It is important to consider that during childhood, many other conditions can result in prolonged SE, including febrile seizures and febrile SE. Genetic disorders such as Dravet syndrome and Alpers syndrome usually involve fever-associated SE. Therefore, a differential diagnosis should include genetic conditions associated with fever-induced epilepsy, such as in SCN1A-, PCDH19-, or POLG1-related epilepsies (Table 2) [2].

**Management**

**1. Acute phase**

The treatment of FIRES represents a significant challenge for clinicians, and is associated with low success rates, especially during the acute phase. There is no evidence of efficacy for any treatment modality except for a ketogenic diet (KD), intravenous immunoglobulin (IVIG), and burst-suppression coma with barbiturates [23]. Multiple different therapeutic options have been reported in small case series demonstrating that no one treatment is superior (Table 3). First-line and second-line immunotherapies, such as...
high-dose intravenous steroids, IVIGs, and plasmapheresis, may be useful, although efficacy is still debated. The efficacy of tacrolimus, rituximab and/or cyclophosphamide is unclear, although there are some reports of improvement in patients who failed other immunotherapies [18,19,24].

In most cases, first-line treatment of SE consists of benzodiazepines (lorazepam, diazepam, midazolam, clonazepam), followed by standard anticonvulsant drugs [4]. These drugs are available in intravenous forms, including phenytoin, phenobarbital, levetiracetam, valproic acid, and lacosamide (for focal SE) [25]. Second-line treatments usually require pharmacological coma with an anesthetic infusion of midazolam and barbiturates (pentobarbital in the United States and thiopental in Europe) [26]. Midazolam appears as effective as thiopental but is associated with fewer adverse events and better long-term neurological outcomes [27]. High doses of phenobarbital have also been proven effective and elicit fewer side effects than anesthetics [2]. Other anesthetic agents, such as propofol, are used in the management of refractory SE, though its prolonged use in children is discouraged due to the risk of propofol infusion syndrome, a fatal complication occurring when doses of propofol exceed 4 mg/kg/hr for more than 48 hours. Propofol infusion syndrome’s typical features (hypertriglyceridemia, fever, hepatomegaly, or heart failure) are often missing, and other features (arrhythmia, electrocardiographic changes) occur late [28]. Tapering from anesthetics is very difficult and seizure recurrence is common. Moreover, there are concerns regarding anesthetics’ use in FIRES, since prolonged burst-suppression coma has a significant association with a worse cognitive outcome and with a more severe course of disease [2]. Medications with an IV formation are favored, but topiramate, pregabalin, and/or clobazam are sometimes used later as add-on therapy.

The KD has been used successfully in patients with refractory seizures and, according to some reports, has shown some efficacy in FIRES (Table 4) [4,29,30]. It has been hypothesized that the KD may not only have an anticonvulsant effect (e.g., through the production of decanoic acid, which induces a direct inhibition of the post-synaptic excitatory AMPA) but also an anti-inflammatory effect. Early introduction of a KD in children with FIRES could be effective not only during the acute phase but also in long-term epilepsy management and cognitive outcomes [2]. It is hoped that future prospective controlled studies can confirm the efficacy of KD in the treatment of FIRES.

Because inflammation is presumed to play a causal role in FIRES, approaches that modulate the immune system have been employed. However, these treatments have not been systematically studied. High-dose intravenous steroids are often used [31]; however, this treatment is associated with significant adverse effects. Treatment with IVIG is being explored as an option, but its efficacy has not been demonstrated [32]. The efficacy of plasmapheresis has also not been demonstrated [32]. Other agents, such as anakinra, a recombinant, modified version of the human interleukin-1 receptor antagonist protein, have been effective in some patients, both in the acute phase and in the prevention of adverse outcomes [33]. Tocilizumab is a humanized monoclonal antibody against the interleu-
Seizure outcome of KD

Patients with refractory SE

- Treatment of KD
  - 4 Patients were treated with KD
    - 4:1 KD intravenous infusion (with prior AEDs)
  - Prior AEDs (median number, 3.5; median duration, 18 days)

Seizure outcome of KD

- 1 Patient: seizures stopped within 2–4 days following the initiation of KD (one responder: early stop of KD, followed by relapse of SE and death)
- 9 Of 10 patients: resolution of SE in a median of 7 days after KD initiation
- 8 Of 9 patients: weaned off anesthesia within 15 days of KD initiation
- 1 Of 10 patients: side effects

KD, ketogenic diet; FIRES, febrile infection-related epilepsy syndrome; SE, status epilepticus; AED, antiepileptic drug.

*Underlying causes of SE: immune-mediated encephalitis, LGS, non-ketotic hyperglycinemia, genetic epilepsy, new-onset refractory status epilepticus (NORSE), and FIRES.

Table 4. Previous literature on the therapeutic effects of KD in patients with FIRES

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment of KD</th>
<th>Seizure outcome of KD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kramer et al. (2011)</td>
<td>77 Patients with refractory SE and preceding febrile infection</td>
<td>4 Patients were treated with KD</td>
<td>1 Patient: seizures stopped within 2 days after KD</td>
</tr>
<tr>
<td>Nabbout et al. (2010)</td>
<td>9 Patients with FIRES (age, 54–98 mo)</td>
<td>4:1 KD intravenous infusion (with prior AEDs)</td>
<td>7 Patients: efficacious within 2–4 days following the initiation of KD (one responder: early stop of KD, followed by relapse of SE and death)</td>
</tr>
<tr>
<td>Appavu et al. (2016)</td>
<td>10 Children with super-refractory SE (age, 2–16 yr)</td>
<td>Prior AEDs (median number, 3.5; median duration, 18 days)</td>
<td>9 Of 10 patients: resolution of SE in a median of 7 days after KD initiation</td>
</tr>
</tbody>
</table>

Cannabidiol (CBD) works by decreasing glutamate and gamma-aminobutyric acid synaptic transmission in the brain. The resultant decrease in excitatory neurotransmitter release may increase the seizure threshold [36]. In a recently published case series, CBD appeared effective in reducing the frequency and duration of seizures in patients with FIRES who had not responded to standard AEDs or other therapies [37]. Magnesium infusions are generally not efficacious, but there are isolated reports of good seizure control in children with FIRES after continuous intravenous infusion of magnesium sulfate [38]. In these children, serum magnesium concentrations ranging from 2.1 to 5 mmol/L were achieved. No significant adverse effects were observed.

Therapeutic hypothermia may also be effective in the control of SE by reducing proinflammatory cytokine levels and protecting the integrity of the blood-brain barrier [5]. Preliminary data showed that therapeutic hypothermia at 33°C may be effective in the control of SE [5]. Vagus nerve stimulation (VNS) is typically introduced as long-term treatment for seizure control after recovery from SE. A recent retrospective review reported the effect of VNS in controlling SE in children, and found that VNS appeared to have a favorable effect on SE, NORSE and generalized convulsive seizures in children with post-FIRES medically intractable epilepsy [39].

2. Chronic phase

No systematic study exists for treatment of FIRES in the chronic phase. Despite polytherapy, the severity and frequency of seizures increase intermittently and during infections, again resulting in SE. If FIRES is inflammation-mediated, the anti-inflammatory effects of CBD or anakinra may have anti-seizure effects not only in the acute but also in the chronic phase of illness [37]. Additionally, we found that KD, clonazepam, and phenobarbital are often employed as therapeutic options during the chronic phase [40].

Prognosis

The prognosis following FIRES is poor. The seizures are recalcitrant, prolonged, and difficult to control [41]. No therapeutic modality is efficacious in shortening the acute phase, with the exception of KD. Outcomes appear to be better when the KD is used early and if KD is effective in producing better outcomes. Therefore, the prognosis may improve due to both earlier diagnosis and earlier KD [42]. Mortality associated with FIRES is 10% during the acute phase and 13% during the chronic phase [7]. Only one-third of the surviving patients had normal or borderline cognitive level; one-third had mild-to-moderate intellectual disability, and one-third had severe mental retardation or were in a vegetative state. Nearly all patients had refractory epilepsy at follow-up. Cognitive levels at follow-up were significantly related to the duration of burst-suppression coma and younger age at onset of FIRES [43]. The presence of higher signal periventricular white matter lesions may be correlated with poorer neurological outcomes [7]. However, very few long-term observations exist to date.

Conclusions

FIRES is a rare epilepsy syndrome of unclear etiology in which children, usually of school age, suddenly develop very frequent sei-
The majority of children with FIRES are left with significant cognitive disability and refractory epilepsy. Treatments have poor efficacy, and therefore new insights concerning FIRES pathogenesis are still desperately needed in order to develop more targeted therapies.

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

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Authors’ contributions
Conceptualization: YJL. Data curation: YJL. Formal analysis: YJL. Project administration: YJL. Visualization: YJL. Writing-original draft: YJL. Writing-review & editing: YJL.

References


Clinical Differences between Enterovirus and Human Parechovirus in Children and Infants

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Introduction

Aseptic meningitis is commonly caused by enterovirus (EV) infection, which is mostly a benign pathogen with a few exceptions in all ages, especially in children [1-3]. Human parechovirus (HPeV) previously belonged to the enterovirus genus in the Picornaviridae family but was re-classified to the parechovirus genus [4]. HPeVs share many biological, clinical, and epidemiologic characteristics with EVs [5-7]. Both viruses are also common potential pathogens for neonatal febrile disease [8,9] and febrile disease with upper respiratory tract infection or viral exanthema [10]. Both viruses are transmitted via the fecal-to-oral route and all age groups are susceptible. Although both viruses have similar clinical symptoms, some studies have reported difficulty in differentiating them based on their clinical characteristics alone, especially in young infants without symptoms [3].

Both EV and HPeV infections have similar clinical findings and are the main leading causes of meningoencephalitis (ME) in neonates, and can sometimes cause fatal diseases, especially in infants and neonates. EV infections, especially those of the E71 virus, have been reported to be fatal in children, with few cases of endemic encephalitis and brain stem encephalitis. Recently, HPeV has also been reported to cause white matter disease in neonates with some cases being fatal [5,11-13] or having a poor prognosis in the long
This study aimed to compare the clinical aspects of EV and HPeV infections. Moreover, the findings of this study will help to better manage patients and their treatment and inform future studies.

Materials and Methods

1. Patient enrollment, study population, and study design
This retrospective chart review study was performed on children who underwent cerebrospinal fluid (CSF) examination in the CHA Bundang Hospital for ME diagnosis due to fever or neck stiffness symptoms from 1st June 2018 to 31st August [10,14-17]. We enrolled 228 patients all below 15 years of age who underwent lumbar puncture. The exclusion criteria were: (1) incomplete CSF studies such as traumatic tap; (2) non-meningitis causes of fever with a defined alternative fever focus; or (3) lumbar puncture for diagnosis of metastatic cancer or for delivering cancer medication (Fig. 1). After exclusion, 161 samples were analyzed for the detection of virus using Film Array® ME panel (bioMerieux SA, Marcy-l’Étoile, France). Among these samples, 50 were positive for either HPeV or EV, and we compared the clinical symptoms, laboratory findings, treatment, and prognosis of the corresponding patients.

2. Demographical characteristics and clinical/laboratory information
We retrospectively reviewed the medical records of the HPeV- and EV-positive patients and collected data such as age, sex, symptoms (e.g., duration of fever, presence of vomiting, headache, and irritability), and treatment (e.g., administration of hypertonic fluid [mannitol] and immunoglobulin). Furthermore, we collected their laboratory results such as hemoglobin, white blood cell (WBC) count and its differential count, platelet count, and erythrocyte sedimentation rate (ESR) as well as CSF examination findings such as CSF total and differential WBC count, pH, protein levels, and glucose. Subsequently, we adjusted the findings according to age and sex. Lastly, we collected and analyzed brain scan images where available. The CSF WBC was corrected according to the CSF red blood cell (RBC) count if the CSF RBC count was more than 50,000 cells/mm³. In cases where the CSF WBC count was more than 10 cells/mm³, we used the differential WBC count. In cases where the patient underwent multiple lab tests, such as for C-reactive protein (CRP) and WBC count, the highest values were used for statistical evaluation.

3. Virus detection in CSF study: ME panel
We assessed the CSF samples for the viruses using the Film Array® ME panel from bioMerieux, which requires 200 μL of CSF and takes about an hour to complete. We used freeze-dried reagents to detect the nucleic acids of the particular pathogens. This method allowed detection of all species of EV (A–D) and several serotypes of human EV including EV71, EV68, coxachieviruses, and echoviruses. Moreover, it allowed detection of HPeV serotypes 1–6 [18].

4. Statistical analysis
Data were analyzed using the chi-square test, Fisher’s exact t-test, Mann-Whitney test, and multiple logistic or linear regression using SPSS version 23.0 (IBM Co., Armonk, NY, USA). Multivariable regression models were used to estimate the adjusted odds ratios and 95% confidence intervals adjusted for age and sex. A P value of less than 0.05 was considered statistically significant. The Mann-Whitney test was used to analyze variables that did not show a standardized distribution after the Kolmogorov-Smirnov test.

5. Ethics statement
The study protocol was approved by the appropriate Institutional Review Board of CHA University (CHAMC-2018-08-011). Informed consent was waived by the board.

Fig. 1. Flow diagram of the inclusion process of participants in this study. CSF cerebrospinal fluid; ME, meningoencephalitis; HHV6, human herpesvirus 6.
Results

1. Demographic findings
Samples from a total of 161 patients (males 96, females 65) were examined using film array-ME and 50 patients were positive for EV or HPeV infections (Fig. 1). Among the 50 patients, 36 were positive for EV (one also had rotavirus-positive stool) and 14 were positive for HPeV (one also had varicella-zoster virus). The proportion of males with EV and HPeV infections were 19 of 36 (52.8%) and six of 14 (42.9%), respectively (P=0.671). Patients with EV infection were older than those with HPeV infection (median 27 [interquartile range, IQR, 3 to 77] and 2 months [IQR, 2 to 3], respectively; P=0.000) (Table 1).

2. Clinical symptoms
There was no significant difference in the total fever duration between the EV and HPeV group (29.2 [IQR, 22.0 to 58.5] and 37.3 hours [IQR, 26.0 to 5.0], respectively; P=0.713). Headache and

Table 1. Demographic and clinical characteristics of children with enterovirus or human parechovirus infections with and without adjustment for age and sex

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>Enterovirus (n = 36)</th>
<th>Parechovirus (n = 14)</th>
<th>P value</th>
<th>OR (95% CI)</th>
<th>Adjusted for age and sex</th>
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<tr>
<td>Clinical data</td>
<td></td>
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<tr>
<td>Age (mo)</td>
<td>50</td>
<td>27 (3–77)</td>
<td>2 (2–3)</td>
<td>0.000*</td>
<td>0.754</td>
<td>0.671 (0.193 to 2.329)</td>
</tr>
<tr>
<td>Male sex</td>
<td>50</td>
<td>19 (52.8)</td>
<td>6 (42.9)</td>
<td>0.368</td>
<td>0.713</td>
<td>0.671 (0.193 to 2.329)</td>
</tr>
<tr>
<td>Symptom</td>
<td></td>
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<tr>
<td>Fever</td>
<td>50</td>
<td>34 (94.4)</td>
<td>14 (100)</td>
<td>0.368*</td>
<td>1.412</td>
<td>0.999 (0.000 to 2.000)</td>
</tr>
<tr>
<td>Fever duration above 38°C (hr)</td>
<td>50</td>
<td>29.2 (22.0–58.5)</td>
<td>37.3 (26.0–53.0)</td>
<td>0.713*</td>
<td>0.632</td>
<td>4.306 (−13.647 to 22.260)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>50</td>
<td>12 (33.3)</td>
<td>7 (19.9)</td>
<td>0.589*</td>
<td>0.481</td>
<td>7.468 (−13.667 to 28.603)</td>
</tr>
<tr>
<td>Headache</td>
<td>50</td>
<td>15 (41.7)</td>
<td>0</td>
<td>0.004*</td>
<td>0.999</td>
<td>0.000 (0.000 to 0.000)</td>
</tr>
<tr>
<td>Irritability</td>
<td>50</td>
<td>2 (5.6)</td>
<td>0</td>
<td>0.368*</td>
<td>0.998</td>
<td>0.000 (0.000 to 0.000)</td>
</tr>
<tr>
<td>ICP (cmH2O)</td>
<td>17</td>
<td>14.35 ± 8.46</td>
<td></td>
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</tbody>
</table>

Laboratory findings of serum samples

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>Enterovirus (n = 36)</th>
<th>Parechovirus (n = 14)</th>
<th>P value</th>
<th>OR (95% CI)</th>
<th>Adjusted for age and sex</th>
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</tr>
<tr>
<td>WBC (/μL)</td>
<td>50</td>
<td>10,851 ± 3,064</td>
<td>5,366 ± 1,958</td>
<td>0.015*</td>
<td>0.000</td>
<td>–5,275.6 (−7,764.6 to −3,274.8)</td>
</tr>
<tr>
<td>Seg (%)</td>
<td>50</td>
<td>66.5 (38.2–84.5)</td>
<td>55.0 (43.0–64.0)</td>
<td>0.510*</td>
<td>0.004</td>
<td>14.973 (4.910 to 25.037)</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>50</td>
<td>0.3 (0.08–0.90)</td>
<td>0.22 (0.09–0.62)</td>
<td>0.634*</td>
<td>0.946</td>
<td>–0.019 (−0.591 to 0.552)</td>
</tr>
<tr>
<td>Procalcitonin (ng/mL)</td>
<td>29</td>
<td>0.09 (0.07–0.10)</td>
<td>0.12 (0.09–0.19)</td>
<td>0.028*</td>
<td>0.093</td>
<td>0.125 (−0.023 to 0.272)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>50</td>
<td>12.1 ± 1.1</td>
<td>11.2 ± 2.7</td>
<td>0.236*</td>
<td>0.638</td>
<td>–0.256 (−1.344 to 0.832)</td>
</tr>
<tr>
<td>Platelet (10^3/μL)</td>
<td>50</td>
<td>365 ± 108</td>
<td>385 ± 113</td>
<td>0.557*</td>
<td>0.322</td>
<td>–34.560 (−103.999 to 34.878)</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>20</td>
<td>13 (10–28)</td>
<td>13 (6–18)</td>
<td>0.484*</td>
<td>0.941</td>
<td>–0.722 (−21.033 to 19.588)</td>
</tr>
</tbody>
</table>

Laboratory findings of CSF samples

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>Enterovirus (n = 36)</th>
<th>Parechovirus (n = 14)</th>
<th>P value</th>
<th>OR (95% CI)</th>
<th>Adjusted for age and sex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>50</td>
<td>7.5 (7.0–7.5)</td>
<td>7.5 (7.0–7.5)</td>
<td>0.481*</td>
<td>0.639</td>
<td>–0.060 (−0.315 to 0.195)</td>
</tr>
<tr>
<td>RBC (f/m^3)</td>
<td>50</td>
<td>3 (1–35)</td>
<td>1 (0–173)</td>
<td>0.199*</td>
<td>0.577</td>
<td>–1,347.6 (−6,176.9 to −3,481.8)</td>
</tr>
<tr>
<td>WBC (f/m^3)</td>
<td>50</td>
<td>30 (4–153)</td>
<td>2 (1–5)</td>
<td>0.001*</td>
<td>0.018</td>
<td>−259.5 (−471.8 to −47.2)</td>
</tr>
<tr>
<td>Seg (%)</td>
<td>21</td>
<td>31.3 ± 25.6</td>
<td></td>
<td></td>
<td>0.621</td>
<td>0.015 (−0.007 to 0.077)</td>
</tr>
<tr>
<td>Protein (mg/dL)</td>
<td>50</td>
<td>42.8 ± 21.7</td>
<td>47.9 ± 15.1</td>
<td>0.426*</td>
<td>0.552</td>
<td>–3.837 (−16.715 to 9.041)</td>
</tr>
<tr>
<td>Glucose ratio (CSF/serum)</td>
<td>50</td>
<td>0.57 ± 0.09</td>
<td>0.56 ± 0.08</td>
<td>0.606*</td>
<td>0.621</td>
<td>0.015 (−0.007 to 0.077)</td>
</tr>
</tbody>
</table>

Treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>Enterovirus (n = 36)</th>
<th>Parechovirus (n = 14)</th>
<th>P value</th>
<th>OR (95% CI)</th>
<th>Adjusted for age and sex</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVIG</td>
<td>50</td>
<td>8 (22.2)</td>
<td>10 (71.4)</td>
<td>0.002*</td>
<td>8.750</td>
<td>8.127 (35.507 to 8.882)</td>
</tr>
<tr>
<td>Manntiol</td>
<td>50</td>
<td>17 (47.2)</td>
<td>1 (7.1)</td>
<td>0.009*</td>
<td>3.951</td>
<td>17.142 (18.888 to 8.882)</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range), number (%), or mean±standard deviation.
OR, odds ratio; CI, confidence interval; aOR, adjusted OR (adjusted with age and sex, reference value is enterovirus); B, coefficient; ICP, intracranial pressure; WBC, white blood cell count; seg, fraction of the segmented cell; CRP, C-reactive protein; ESR, erythrocyte sedimental rate; CSF, cerebrospinal fluid; RBC, red blood cell; IVIG, intravenous immunoglobulin.

*P value with Mann-Whitney test; †P value with Pearson’s test; ‡Adjusted odds ratio with logistic regression analysis, fever duration 38°C and 37.5°C; ¶With linear regression analysis; §P value with independent t-test.

https://doi.org/10.26815/acn.2019.00227
vomiting were more prevalent in the EV group \((P = 0.004\) and \(P = 0.058\)) while there was no significant between-group difference in irritability \((P = 0.708)\). After adjusting for age and sex, there were no significant between-group differences in symptoms such as headache, vomiting, duration of fever, and irritability \((P = 0.999, P = 0.397, P = 0.632,\) and \(P = 0.998,\) respectively).

3. Laboratory findings
The serum WBC count was higher in the EV group than in the HPeV group \((10,851 \pm 3,064 vs. 5,366 \pm 31,953, P = 0.015)\). The CSF study was conducted within 24 hours of admission which means that the CSF study was performed within 2 to 3 days of symptom (fever) onset (totally 0 [IQR, 0 to 0.5]; EV 0 [IQR, 0 to 1]; HPeV 0 [IQR, 0 to 0]; \(P = 0.068\)). There were no significant between-group differences in the segmented cell dominancy, CRP, and ESR \((P = 0.510, P = 0.634,\) and \(P = 0.484,\) respectively); however, procalcitonin was higher in HPeV \((EV 0.09 [IQR, 0.07 to 0.10] vs. HPeV 0.12 [IQR, 0.09 to 0.19], P = 0.028)\). The CSF WBC count was higher in the EV group than in the HPeV group \((30 [IQR, 4 to 153] vs. 2 [IQR, 1 to 5], P = 0.001)\); however, there were no significant between-group differences in the CSF RBC, glucose, and protein levels. After adjusting for age and sex, the CSF and blood WBC count was lower in the HPeV group than in the EV group \((CSF WBC count \sim259.53 [IQR, \sim471.8 to \sim47.2], P = 0.018; WBC count in blood \sim5,275.6 [IQR, \sim7,276.4 to \sim3,274.8], P = 0.000)\).

4. Treatment
Regarding treatment, the use of hyperosmotic fluid (mannitol) was higher in the EV group \((P = 0.009)\) while the use of immunoglobulin was higher in the HPeV group \((P = 0.002)\). Immunoglobulin was administered to 18 patients while the number of children treated with different intravenous immunoglobulin (IVIG) doses was as follows: four with 0.5 g/kg, seven with 1 g/kg, three with 1.5 g/kg, and four with 2.0 g/kg. After adjusting for age and sex, there was no significant between-group difference in the frequency of usage of mannitol and immunoglobulin.

5. Neurologic symptoms and follow-up
One newborn (female, 40 days old) who tested positive for HPeV had seizures with unilateral semiology, with an electroencephalograph showing a negative sharp wave. Her CSF WBC count was only \(2/mm^3\), and multifocal small hyperintensities were observed using diffusion-weighted magnetic resonance imaging (MRI) of the bilateral cerebral white matter \((Fig. 2A\) and \(B)\). A week after IVIG management, follow-up MRI indicated improvement in this newborn with unilateral seizure. The anticonvulsive drug (phenobarbital) dose was gradually reduced after which she showed no symptoms. Moreover, all the patients showed normal development without symptoms at the 12-month follow-up. A 46-day-old female with EV infection had fever, and CSF WBC count was 1,780/mm\(^3\) \((Fig. 2C\) and \(D)\). She also underwent brain MRI and had a small hyperintense region in white matter on diffusion weighted MRI. She was administered with IVIG and improvements in her symptoms were noted. Until the age of 8 months, she showed normal development. Another 19-month-old male with simple febrile seizures tested positive for EV and the CSF WBC count was \(1/mm^3\); there were no further neurologic symptoms. Lastly, a 55-month-old male who tested positive for EV presented with...
atatic gait without fever. He had no vomiting or headache and a CSF WBC count of 23/mm³. Brain MRI was normal and spine MRI, which was performed after symptom improvement, was unremarkable. No relapse occurred during the 8-month follow-up period.

6. Image study and further neurologic study
Computed tomography (CT) scans were done in 18 EV-infected patients, five patients (three EV-infected, two HPeV-infected) underwent MRI, and three HPeV-infected patients underwent cranial ultrasonography. A total of 25 patients did not undergo brain imaging or electrophysiologic studies. Among those who underwent CT and cranial ultrasonography, none showed gross abnormalities, and a baby showed mild periventricular leukomalacia. Among the five patients who underwent MRI examination, two showed abnormal findings of high signal intensity on diffusion-weighted magnetic resonance images in the white matter of a relatively short duration that was fully reversible (Fig. 2).

Discussion
Both EVs and HPeVs belong to same viridae [6], have similar clinical aspects, and are common pathogenic causes of aseptic meningitis in young children, as observed in this study. Despite their very similar clinical characteristics, we found that HPeV is more common among neonates and that patients with HPeV had a lower CSF and blood WBC count even after adjusting for age and sex. Previous studies have reported clinical [19], neuroimaging [12], and prognostic [6,11], similarities between both viruses. Moreover, there has been a reported male predominance; however, it was not statistically significant [7]. In this study, we could not find differences in the clinical characteristics of HPeV and EV infections, such as headache, vomiting, and irritability.

We found that the CSF WBC count was relatively low in the HPeV group compared with the EV group. Previous studies also reported a low CSF WBC in this group [5,7,20]; however, other studies have not reported this finding [5,9,21]. This result means that patient with lower CSF WBC counts without HPeV assessment were not considered to have meningeal infection, and many of the fever cases with an unknown focus might have possibly resulted from HPeV infection. This is especially the case during summer and early fall [2], where aseptic meningitis caused by HPeV infection might lead to an increase in the cases of febrile children with mild headache. Moreover, there have been reports of infants with unknown fever focuses that were later determined to be caused by this virus [15]. Nearly absent pleocytosis in the CSF, which was previously considered as negative indicator of meningitis, was found in HPeV-infected patients [5,19]. This means that viral meningitis should be suspected even if the WBC count is less than 5 cells/mm³.

The age distribution, specifically the younger age preference of these viruses, as shown in this study, are possibly due to an actual age preference of the HPeVs [14,22] or selection bias due to the relatively mild symptoms in older children. Patients with low immunity are susceptible to viral infection, especially with rotavirus; however, the presence of an intact immune system might deter the process of viral infection. In addition, many patients lack access to or prefer not to undergo lumbar puncture, which can cause selection bias regarding CSF examination, especially given that relatively mild symptoms of aseptic meningitis cannot be detected. Moreover, due to the fecal-to-oral route of infection of this virus, an infant’s siblings could also be infected by this virus. Using non-invasive assessment techniques, such as stool or nasal swab, can correct some of the selection bias.

Treatment of infants with IVIG may prevent brain viral infection from becoming fatal or severe sequelae [23]. Early administration of IVIG has been reported to improve fatal EV infections such as hepatitis with coagulopathy and thrombocytopenia or myocarditis [24]. Abzug et al. [17] also demonstrated that neutralization of EVs using 750 mg/kg IVIG can change the course of encephalitis with rapid cessation of viremia and can improve the prognosis. Moreover, other studies [12,15,19,25,26] have also reported the use of IVIG for prevention of possibly fatal cases of neonatal HPeV infection. Further studies are required on the use of IVIG in the treatment of HPeV infection to improve the infantile HPeV/EV management protocol. A few patients with HPeV infections also presented with white matter injury and the infection was transiently observed with a benign course; however, previous studies have reported neonatal HPeV infections with a fatal course [11,12,19]. We found less serious pathogenicity of HPeV compared to that reported by a previous study [12], which might be attributed to the use of IVIG therapy. The fatality of neonatal viral infection may be due to viral subdivision, which was not studied in this study. Moreover, it might be influenced by the use of IV globulin in the early disease course. However studies with long-term follow-up are needed to confirm this.

This study has several limitations. As previously mentioned above, older children with mild symptoms did not undergo lumbar puncture, which possibly resulted in selection bias. An early CSF study can show a low WBC count, which then increased during the subsequent few days. Moreover, we did not perform MRI examinations on babies with neurologic symptoms or CT and cranial ultrasonography in children/babies with mild symptoms; therefore, we might have missed cases with white matter injury. Diffu-
sion-weighted MRI image can detect white matter injury resulting from HPeV encephalitis [12]. In addition, we only conducted this study for a period of one season in one year; therefore, there is a need for studies with more participants and a longer study period [10,18,21]. Moreover, we could not determine the subtype classifications of the EVs and HPeVs [27], which is important given the different fatalities of each subclass of the viruses [4]. Lastly, since we only used one study method to assess the samples, there is a possibility of false positives and negatives.

We found that HPeV and EV infection have similar clinical characteristics and mostly similar laboratory values. However, we found between-group differences in the predominant age and CSF and blood WBC count with the CSF WBC count in HPeV patients being less than the cut-off value for aseptic meningitis. Therefore, we should consider assessing for viral infection even when the CSF WBC count is low. Lastly, MRI examination can help in the positive diagnosis of EV and HPeV infections, especially in infants.

Conflicts of interest

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

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Author contributions

Conceptualization: SR. Data curation: SR. Formal analysis: SR. Funding acquisition: SR. Methodology: SR. Project administration: SR. Visualization: SR. Writing-original draft: SR. Writing-review & editing: SR.

References


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Purpose: Nonepileptic paroxysmal events (NPEs) are common in infancy and may be misinterpreted as epileptic seizures. With a knowledge of common NPEs, they can usually be diagnosed based on a detailed history and examination. So far, no studies have explored the semiological presentations of NPEs in infancy without video electroencephalographic (VEEG) recordings. We aimed to describe the phenomenology of NPEs in infancy to provide useful information to clinicians, enabling easier diagnoses without VEEG studies.

Methods: We reviewed the medical records of 63 patients aged from 1 to 12 months diagnosed with NPEs at Daegu Catholic University Medical Center from September 2006 to June 2017. We classified the phenomenological features into five types: abnormal body movement, eye changes, breathing abnormalities, behavioral symptoms, and autonomic symptoms.

Results: Of the 63 patients, 37 were male and 26 were female. The mean age at onset was 6 months, and the mean duration of symptoms was 22.5 days. Abnormal body movements were the most common feature (88.9%), followed by eye changes (31.7%), autonomic symptoms (11.1%), breathing abnormalities (6.3%), and behavioral abnormalities (3.2%). The most common type of abnormal body movements was shivering-like movement (32.1%). Initially, 30 patients (47.6%) were diagnosed with unclassified NPEs, nine (14.3%) with sleep myoclonus, six (9.5%) with benign paroxysmal tonic upward gaze, and five (7.9%) with benign myoclonus of infancy. During follow-up, two patients (3.2%) were diagnosed with epilepsy.

Conclusion: Knowledge of the phenomenological characteristics of NPEs in infancy can be useful for making a correct diagnosis.

Keywords: Seizures; Dyskinesias; Infant

Introduction

Nonepileptic paroxysmal events (NPEs) are characterized by seizure-like behaviors without concomitant ictal electroencephalography (EEG), and common in infancy [1,2].

According to Visser et al. [3], the incidence of paroxysmal disorders in infancy is 8.9%, of which 52% are physiological events. NPEs may be misinterpreted as epileptic seizures, which is likely to cause alarm amongst parents and concern amongst professionals. The range of possible diagnoses for a paroxysmal disorder in infancy is extensive. A number of these conditions are benign and often physiological in many cases, such as neonatal tremor, benign neonatal sleep myoclonus, and shuddering attacks [2,4]. Accurate diagnosis is crucial for avoiding unnecessary evaluation and medica-
tion, and alleviating parents’ worries [2,5-7]. Diagnosis can usually be made based on detailed history and examination, with the knowledge of several types of NPEs with distinctive clinical presentations [5,7]. However, differentiation between true seizures and NPEs is difficult during infancy due to variations in semiology and incorrect history provided by parents or caregivers. Because of these difficulties, video electroencephalographic (VEEG) recording is required for a definitive diagnosis [6,8]. Although VEEG recording is the most accurate diagnostic method, it is difficult to perform in infants, and cannot easily be performed in all medical centers [5]. Due to widely available smartphones, mobile phone video can be used as an important diagnostic tool before proceeding to VEEG recording. Although there are several reports of NPEs with VEEG recordings in children, there are no reports of the various semiological presentations of NPEs in infancy without VEEG study.

We aimed to describe the phenomenology of NPEs in infants to provide clinicians with useful information for more accurate and easier diagnosis, without VEEG recording.

Materials and Methods

After Institutional Review Board approval (CR-17-086-L), we retrospectively reviewed the medical records of 63 children aged from 1 to 12 months, diagnosed with NPEs, or pseudoseizure, between September 2006 and June 2017 at Daegu Catholic University Medical Center. Written informed consent by the patients was waived due to a retrospective nature of our study. We analyzed sex, age, age at onset, duration of symptoms before seeking medical attention, frequency, form of main symptom, situation of occurrence, responsiveness to stimulation during the event, preceding event, gestational age, developmental history, family history, associated medical conditions, electrocardiogram (ECG), EEG, brain imaging, initial and final diagnosis. As for the frequency of events at the initial visit, we included even a single episode, because NPEs can happen as a single episode. Based on semiological features, the main symptoms were categorized into five types as follows: abnormal body movement, eye changes, breathing abnormalities, behavioral, and autonomic symptoms. Abnormal body movements included any type of facial or bodily movements. Eye changes included eye deviation, blinking, nystagmus, fixed pupils, and opening wide. Breathing abnormalities included apnea and irregular coarse respiration. Behavioral symptoms included staring and arrest of activity. Autonomic features included retching, drooling, facial color changes, and tachycardia. Although the phenomenologic character was categorized by main symptoms, many patients had multiple simultaneous features. Therefore, we also analyzed all semiological descriptions. The situation of occurrence was categorized as follows: playing, sleeping, feeding, sleepy, awakening, specific position or crying. Responsiveness was defined as changes in the event upon stimulation. Additional work ups including blood tests, ECG, EEG, and brain imaging were performed when there was a clinical suspicion for seizures based on history. The initial diagnosis was made by the physician at the first encounter based on clinical information, and the final diagnosis was made at a later date, after a period of follow-up. Highly suspecting epileptic seizures were termed as epilepsy in the initial diagnosis lists.

**1. Definitions of conditions mimicking epileptic seizures**

- Apparent life-threatening events (ALTE) or brief resolved unexplained events: an episode that is frightening to the observer and characterized by some combination of apnea, color change, marked change in muscle tone, choking or gagging [4,9].
- Benign paroxysmal vertigo (BPVC): migraine equivalent, consisting of episodes of vertigo lasting from a few seconds to minutes, that is often accompanied by postural imbalance and nystagmus [9].
- Startle response: also known as the startle reflex and the alarm reaction. The alarm reaction is a completely natural, involuntary reaction to a stimulus such as a flash of light, sudden threatening movement or loud noise [4,9].
- Benign paroxysmal tonic upward gaze (PTU): protracted attacks (hours to days) of continuous or episodic upward gaze deviation, during which horizontal eye movements are preserved [7,9,10].
- Sleep myoclonus: repetitive, usually bilateral rhythmic jerks involving the upper and lower limbs during nonrapid eye movement sleep, sometimes mimicking clonic seizures [4,7,9,10].
- Benign myoclonus of infancy (BMI): myoclonic jerks of the extremities during wakefulness and sometimes also during sleep [2,9].
- Shuddering attacks: rapid tremor of the head, shoulder, and trunk, lasting a few seconds, often associated with eating and recurring many times a day [9].
- Benign paroxysmal torticollis of infancy (BPT): painless retrocollis, and later, torticollis, often triggered by changes in posture [2,7,9,10].
- Unclassified NPEs: unclassified infantile behavior (age related behavior, pseudoseizure) [2].

**2. Data analyses**

This descriptive study used mean, maximum and minimum for the two continuous variables and frequency to describe discontin-
uous variables.

Results

1. Demographic and clinical characteristics

Of the 63 patients, 37 (58.7%) were male and 26 (41.3%) were female, mean age at onset was $5.6 \pm 2.9$ months (range, 1 to 11), and mean duration of symptoms was $22.5 \pm 28.3$ days (range, 1 to 90). Each one (1.6%) had one of the following preceding events before symptom onset: vaccination, febrile seizure, and bronchiolitis. Family history of febrile seizure, epilepsy, and migraine was each present in one patient (1.6%). Ten patients (16%) had associated medical conditions, including developmental delay, constipation, bilateral sensorineural hearing losses with hypotonia, the chromosomal abnormality 47, XY,+der(22)t(11;22)(q23.3;q11.2), laryngomalacia, febrile seizure, hemophilia, or periventricular leukomalacia.

In 27 infants (42.9%), events occurred daily. Twenty-three (37%) showed responsiveness to external stimuli. Events most commonly occurred when playing (58.7%). Twenty-four patients (38.1%) underwent EEG and four (6.3%) showed abnormal results. Neuroimaging was performed in five patients (7.9%), and none had abnormal findings (Table 1).

2. Phenomenology of nonepileptic paroxysmal events

According to main symptom categories, abnormal body movement was the most common and present in 50 patients (79.4%). Patient numbers in the other categories were as follows: seven had eye changes (11.1%), four had breathing abnormalities (6.4%), one had behavioral symptoms (1.6%), and one had autonomic symptoms (1.6%). Among 63 patients, 15 (23.8%) had a mixture of symptoms from different categories. Overall, 56 patients (88.9%) had abnormal body movements, 20 patients (31.7%) had eye changes, and four patients (6.3%) had breathing abnormalities. Seven patients (11.1%) had autonomic symptoms, with facial color change being the most common. Staring was the only behavioral symptom observed, occurring in two patients (3.2%). Two patients (3.2%) had vocalization symptoms such as making ‘mmmm’ sounds and shouting, which were accompanied by other symptoms.

For the phenomena of abnormal body movements, shivering-like movement was the most common (18/56 patients, 32.1%). For ocular symptoms, eyeball deviation was the most common (10/20 patients, 50.0%), and six patients (6/20 patients, 30.0%) had isolated eye changes (Tables 2 and 3).

3. Initial and final diagnoses of NPEs

For the initial diagnoses, 30 patients (47.6%) were diagnosed with unclassified NPEs, nine (14.3%) with sleep myoclonus, six (9.5%) with PTU, five (7.9%) with BMI, three (4.8%) with ALTE, two (3.2%) with shuddering attack, two (3.2%) with BPVC, one

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**Table 1. Clinical characteristics of 63 patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Frequency of events</td>
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<tr>
<td>One or two</td>
<td>13 (20.6)</td>
</tr>
<tr>
<td>Daily</td>
<td>27 (42.9)</td>
</tr>
<tr>
<td>Occasionally</td>
<td>22 (34.9)</td>
</tr>
<tr>
<td>Situation of events</td>
<td></td>
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<tr>
<td>Playing</td>
<td>43 (68.2)</td>
</tr>
<tr>
<td>Sleeping</td>
<td>11 (17.4)</td>
</tr>
<tr>
<td>Feeding</td>
<td>7 (11.1)</td>
</tr>
<tr>
<td>When feeling sleepy</td>
<td>6 (9.5)</td>
</tr>
<tr>
<td>Awakening</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Specific position/crying</td>
<td>3 (4.8)</td>
</tr>
<tr>
<td>Electroencephalography</td>
<td>24 (38.1)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>4 (16.6)</td>
</tr>
<tr>
<td>Epileptic discharge</td>
<td>1</td>
</tr>
<tr>
<td>Slow wave</td>
<td>3</td>
</tr>
<tr>
<td>Brain imaging</td>
<td>5 (7.9)</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>2 (3.2)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

**Table 2. Clinical phenomenology of abnormal body movements**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal body movements</td>
<td>56/63 (88.9)</td>
</tr>
<tr>
<td>Shivering-like movement</td>
<td>18/56 (32.1)</td>
</tr>
<tr>
<td>Stiffening</td>
<td>10/56 (17.9)</td>
</tr>
<tr>
<td>Head shaking side to side</td>
<td>6/56 (10.7)</td>
</tr>
<tr>
<td>Myoclonic, startle</td>
<td>6/56 (10.7)</td>
</tr>
<tr>
<td>Clonic</td>
<td>3/56 (5.4)</td>
</tr>
<tr>
<td>Opisthotonic posturing</td>
<td>2/56 (3.6)</td>
</tr>
<tr>
<td>Shrinking</td>
<td>2/56 (3.6)</td>
</tr>
<tr>
<td>Head nodding forward</td>
<td>2/56 (3.6)</td>
</tr>
<tr>
<td>Irregular movement of the extremities</td>
<td>2/56 (3.6)</td>
</tr>
<tr>
<td>Chin movement</td>
<td>2/56 (3.6)</td>
</tr>
<tr>
<td>Atonic, limping</td>
<td>2/56 (3.6)</td>
</tr>
<tr>
<td>Ataxic</td>
<td>2/56 (3.6)</td>
</tr>
<tr>
<td>Torticollis</td>
<td>2/56 (3.6)</td>
</tr>
<tr>
<td>Shoulder shrugging</td>
<td>2/56 (3.6)</td>
</tr>
<tr>
<td>Facial grimacing</td>
<td>2/56 (3.6)</td>
</tr>
<tr>
<td>Tortipelvis</td>
<td>1/56 (1.8)</td>
</tr>
<tr>
<td>Akinetic, frozen, still</td>
<td>1/56 (1.8)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).
Table 3. Clinical phenomenology of other categories

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye changes</td>
<td>20/63 (31.7)</td>
</tr>
<tr>
<td>Deviation</td>
<td>10/20 (50.0)</td>
</tr>
<tr>
<td>Opening wide</td>
<td>4/20 (20.0)</td>
</tr>
<tr>
<td>Blinking</td>
<td>2/20 (10.0)</td>
</tr>
<tr>
<td>Fixed</td>
<td>2/20 (10.0)</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>1/20 (5.0)</td>
</tr>
<tr>
<td>Mixed</td>
<td>1/20 (5.0)</td>
</tr>
<tr>
<td>Autonomic nervous system</td>
<td>7/63 (11.1)</td>
</tr>
<tr>
<td>Facial color change (flushing, pallor)</td>
<td>4/7 (57.1)</td>
</tr>
<tr>
<td>Digestive symptoms (retching, drooling)</td>
<td>2/7 (28.6)</td>
</tr>
<tr>
<td>Cardiovascular (tachycardia)</td>
<td>1/7 (14.3)</td>
</tr>
<tr>
<td>Breathing abnormalities</td>
<td>4/63 (6.3)</td>
</tr>
<tr>
<td>Apnea</td>
<td>3/4 (75.0)</td>
</tr>
<tr>
<td>Irregular and coarse breathing</td>
<td>1/4 (25.0)</td>
</tr>
<tr>
<td>Vocalization</td>
<td>2/63 (3.2)</td>
</tr>
<tr>
<td>Behavioral staring</td>
<td>2/63 (3.2)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

Table 4. Initial and final diagnosis of 63 patients with nonepileptic paroxysmal events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Initial</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unclassified NPEs</td>
<td>30 (47.6)</td>
<td>35 (55.6)</td>
</tr>
<tr>
<td>Sleep myoclonus</td>
<td>9 (14.3)</td>
<td>9 (14.3)</td>
</tr>
<tr>
<td>PTU</td>
<td>6 (9.5)</td>
<td>5 (7.9)</td>
</tr>
<tr>
<td>BMI</td>
<td>5 (7.9)</td>
<td>6 (9.5)</td>
</tr>
<tr>
<td>ALTE</td>
<td>3 (4.8)</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td>Shuddering attack</td>
<td>2 (3.2)</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td>BPVC</td>
<td>2 (3.2)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>BPT</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Startle response</td>
<td>1 (1.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>4 (6.3)</td>
<td>2 (3.2)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

NPE, nonepileptic paroxysmal event; PTU, benign paroxysmal tonic upward gaze; BMI, benign myoclonus of infancy; ALTE, apparent life-threatening events; BPVC, benign paroxysmal vertigo; BPT, benign paroxysmal torticollis of infancy.

Table 5. Characteristics of two patients finally diagnosed with epilepsy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>6 months</td>
<td>5 months</td>
</tr>
<tr>
<td>Phenomenology</td>
<td>Apneic episode with limping, blank stare followed by pallor with dilated pupils and body shaking movements</td>
<td>Sudden upward gaze</td>
</tr>
<tr>
<td>Frequency</td>
<td>Once</td>
<td>Daily</td>
</tr>
<tr>
<td>Duration</td>
<td>1 day</td>
<td>60 days</td>
</tr>
<tr>
<td>During sleep</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Responsiveness</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Gestational age</td>
<td>Full term</td>
<td>Full term</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Past medical history</td>
<td>Febrile seizure</td>
<td>No</td>
</tr>
<tr>
<td>EEG</td>
<td>Yes, IS in the left temporal</td>
<td>Not done</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>Yes</td>
<td>Not done</td>
</tr>
<tr>
<td>Initial diagnosis</td>
<td>ALTE</td>
<td>PTU</td>
</tr>
<tr>
<td>Course</td>
<td>Three focal seizures with impaired awareness developed at 3 and 10 months after initial events</td>
<td>After 1 month, head nodding with flexor spasm developed</td>
</tr>
<tr>
<td>Final diagnosis</td>
<td>Epilepsy</td>
<td>Epilepsy (West syndrome)</td>
</tr>
</tbody>
</table>

EEG, electroencephalography; IS, intermittent slow; MRI, magnetic resonance imaging; ALTE, apparent life-threatening events; PTU, paroxysmal tonic upward gaze.

Discussion

The frequency of NPEs in children admitted to epilepsy centers for monitoring ranges between 3.5% and 43% [1]. As VEEG studies require frequent occurrences of an event and are also very demanding, especially for infants, every effort should be made to reach a diagnosis based on clinical symptoms [6].

Our study provides a detailed description of the phenomenolo-
of NPEs in infants, and useful clinical tips for their differential diagnosis based on clinical information without VEEG study. Because phenomenological features of NPEs in infancy are varied and complex, they are usually classified arbitrarily according to main clinical features even with VEEG study data [5,10].

Therefore, we categorized NPEs in infancy into five types; movement, eye, breathing, behavioral, and autonomic. For comparison with previous studies and discussion purposes, we classified breathing as an autonomic symptom, and eye changes and vocalization as motor symptoms.

1. Clinical phenomena
1) Motor symptoms

Motor phenomena, with paroxysmal features that interrupt normal motor background activity, are frequently observed in infants [7]. Chen et al. [5] found motor symptoms were the most common manifestation of NPEs in children younger than 2 years of age (68.4%). Kim et al. [11] reported that tonic posturing was the most common NPE in infancy, followed by staring. Park et al. [8] also analyzed NPEs in children younger than 6 years of age and found that normal infant behavior (29.2%) was most commonly observed. Moreover, normal infant behaviors, such as repetitive grimacing, mouth twisting, crossing legs with cold sweats, and tonic-clonic arm movements, were prominent in this age group. In the present study, we found abnormal body movement was the most common and present in 89% of patients, which is similar to previous studies. Among them, shivering-like movement was the most common. In clinical practice, there are clues to discriminate epileptic from nonepileptic motor events. Motor symptoms in epileptic seizures are predominantly deviations of the eyes and head, dystonic and tonic posturing of the limbs, clonic, tonic, or myoclonic jerks, and epileptic spasms that account for around 25% of the epileptic symptoms in this age group. Focal motor features, such as version, are not reported in NPEs. In contrast, the motor features in NPEs are inconsistent and include bizarre, irregular, jerking or thrashing movements of the extremities, generalized jerking/flash ing, focal motor activity, complex motor activity, generalized trem or, head-shaking, generalized limpness, eye fluttering/visual blurring, and oromotor activity [5].

Myoclonus is another clinical motor feature that occurs in infants and toddlers with NPEs [5]. According to Fogarasi et al. [12], the presence of nocturnal myoclonus, only during sleep, should encourage the physician toward a diagnosis of NPEs, because children with epilepsy ≤ 2.6 years of age do not have nocturnal symptom predominance, in the absence of a significant medical history.

Eye changes were a major category in our study and 32.1% had ocular symptoms. Among them, eye deviation was the most common. However, there are no published studies describing this phenomenon in detail. Chen et al. [5] described eye changes as motor symptoms and reported three patients (7.9%) with ocular changes such as eye closure, rolling, and blinking.

There were two patients (3.2%) with vocalization in our study. According to Chen et al. [5], oral/verbal features are present in 36.8% of patients, crying (57.1%) being the most common followed by vocalization and sighing. These features have been overlooked in young infants. Although crying during seizures is a well-known feature of infantile spasms, Shuper and Mimouni [6] reported crying in one infant with NPEs, not epilepsy.

2) Behavioral, staring events

Behavioral features have been previously described in 10.4% to 25.5% of children with NPEs, but mainly in the school-aged group and teenagers. Nonepileptic staring spells and arrest of activity are frequent symptoms during NPEs in infants and toddlers as well [5].

Kim et al. [11] reported that staring was present in 5.7% of infants with NPEs. Staring was present in only two patients (3%) in our study. One patient with autonomic features was diagnosed with epilepsy 10 months later.

 Arrest of activity is also a prominent feature of hypomotor seizures in infants and toddlers. Characteristics of hypomotor seizures in this age group are as follows: (1) progression to other focal motor features, generalized seizures, or infantile spasms, and (2) subtle concomitant features, such as chewing or lip smacking, unforced eye movements, head turning, subtle irregular eye blinking, and stereotypical limb movements.

When compared to epileptic seizures, duration of nonepileptic staring was usually brief (< 30 seconds), and children were mostly responsive without crying.

3) Autonomic symptoms

Fogarasi et al. [13] showed that autonomic symptoms are common in childhood focal epilepsies, also appearing in infants and young children. Apnea/bradypnea occurs more frequently in younger children. Autonomic symptoms in infancy are probably overlooked by the observer, rather than absent, given the predominance of motor features [5].

Chen et al. [5] reported that autonomic features were present in 21.1% of patients with NPEs. In most cases, autonomic features accompanied other clinical features, in particular motor and oral/verbal features. Seven patients (11.1%) had autonomic symptoms in our study. All cases included other features similar to those previously reported [5]. We classified breathing abnormalities as an isolated category, although Chen et al. [5] categorized these as au-
tonomic features. Eleven patients (17.4%) had autonomic symptoms, if breathing abnormalities were to be considered autonomic symptoms.

2. Diagnosis

Visser et al. [3] subgrouped paroxysmal events into the broad categories of physiological events, seizures, loss of consciousness, apneic spells, parasomnias, other, and unknown. A large proportion of the disorders (51%) were classified as ‘physiological events,’ which they defined as ‘those that are consistent with the normal pattern of behavior of children that age.’ Chen et al. [5] reported that nonepileptic staring spells and sleep myoclonus were the two most common NPEs in infant and toddlers. Our study revealed that unclassified NPEs was the most common final diagnosis followed by myoclonus, such as benign sleep myoclonus, or BMI. Four infants (6.3%) were initially diagnosed with epilepsy based on clinical information. However, two patients (3.2%) were finally diagnosed with epilepsy, which had a lower incidence than initial impressions. Considering the number of VEEG carried out for NPEs, these findings suggest that detailed clinical information is adequate for making a diagnosis without exacting study [1].

There were several limitations in making a final diagnosis. Because we could only assume some of the conditions mimicking epileptic seizure based on clinical history reported by parents, it was difficult to make a correct diagnosis even after obtaining EEG data. In addition, as we did not follow patients after the initial encounter and presumptive diagnosis, we could not be sure how long NPEs had actually lasted, or whether they had progressed to epilepsy or other neurological problems. Shuper and Mimouni [6] described the clinical phenomenology and resolution time in 13 NPEs patients, reporting that NPEs were present for a period of 2 weeks to 7 months. Based on these data, several weeks of clinical follow-up are recommended, because a significant number of spells will resolve spontaneously. If there is no improvement, further studies are needed, including video EEG recording. Therefore, we strongly recommend some period of observation in order to make a correct final diagnosis.

With advancements in technology such as YouTube and smartphones, it has become easier to observe paroxysmal events of concern, and instruct or educate parents. Moreover, mutations in several genes have recently been associated with some NPEs, such as calcium voltage-gated channel subunit alpha1 A (CACNA1A) in BPT and PTU, glycine receptor subunit alpha-1 (GLRA1) in hyperekplexia, and sodium voltage-gated channel alpha subunit 9 (SCN9A) in paroxysmal extreme pain disorder [2,14,15]. With genetic testing, it is possible to make more accurate diagnoses in clinical practice.

Therefore, we propose that knowledge of NPEs and the differentials between epileptic and nonepileptic events in infancy is useful for guiding clinicians in making the next decision, while avoiding exacting tests, in an outpatient setting.

Conflicts of interest

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

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Author contributions

Conceptualization: KHL. Data curation: HRN and YHK. Formal analysis: HRN, YHK, and KHL. Methodology: HRN, YHK, and KHL. Project administration: KHL. Visualization: HRN, YHK, and KHL. Writing–original draft: HRN. Writing-review & editing: KHL.

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References

6. Shuper A, Mimouni M. Problems of differentiation between epilepsy and non-epileptic paroxysmal events in the first year of
Rituximab is increasingly used as a second-line treatment of neuroinflammatory disorders to improve clinical outcomes in cases refractory to conventional immunotherapy and to reduce relapses. This study aimed to demonstrate the efficacy and safety of rituximab used for pediatric autoimmune neuroinflammatory disorders.

Methods: We retrospectively reviewed the medical records of 32 patients (median age, 8.5 years; range, 1.1 to 17.1; 23 girls) who received rituximab treatment at Seoul National University Children's Hospital. The disease subgroups were anti-N-methyl-D-aspartate (NMDA) receptor (anti-NMDAR) encephalitis (n=11), opsoclonus-myoclonus ataxia syndrome (OMAS) (n=10), other suspected autoimmune encephalitis (n=5), neuromyelitis optica spectrum disorder (n=4), and chronic inflammatory demyelinating polyneuropathy (n=2). Efficacy was measured by modified Rankin Scale (mRS) scores at the initiation of rituximab administration, at 2 months after initiation, and at the last follow-up. A favorable clinical outcome was defined as an improvement of ≥2 in the mRS score or achievement of an mRS score ≤2. Safety was assessed by reviewing infusion-related adverse events and infectious complications, including progressive multifocal leukoencephalopathy.

Results: Two months after the initiation of rituximab therapy, 21 patients (65.6%) had a favorable response, while 26 (82.1%) had a favorable response at the last follow-up. Among the disease subgroups, anti-NMDAR encephalitis and OMAS showed especially good responses. Rituximab infusion-related adverse events were identified in nine patients (28.1%). All complications recovered spontaneously or with only symptomatic treatment.

Conclusion: Rituximab can be used safely for various pediatric autoimmune neuroinflammatory diseases. Rituximab is expected to improve clinical outcomes in pediatric patients with anti-NMDAR encephalitis and OMAS.

Keywords: Rituximab; Anti-N-methyl-D-aspartate receptor encephalitis; Opsoclonus-myoclonus syndrome; Neuromyelitis optica
Introduction

Rituximab is a chimeric monoclonal anti-CD20 antibody that induces B-cell depletion, resulting in a decrease in antibody-mediated immunity [1]. Since it was approved for treatment of non-Hodgkin’s B-cell lymphoma, the indications for use of rituximab have expanded to include diverse autoimmune disorders including rheumatoid arthritis, systemic lupus erythematosus, and nephrotic syndrome [2-5]. In neurology, the use of rituximab in a number of autoimmune neuroinflammatory disorders has increased significantly, including in multiple sclerosis, anti-N-methyl-D-aspartate (NMDA) receptor (anti-NMDAR) encephalitis, opsoclonus-myoclonus ataxia syndrome (OMAS), neuromyelitis optica spectrum disorder (NMOSD), myasthenia gravis (MG), and chronic inflammatory demyelinating polyneuropathy (CIDP) [6-12]. The purposes of rituximab use are either to induce short-term remission in refractory disorders (e.g., NMDAR encephalitis and OMAS) or to prevent the occurrence of relapses (e.g., NMOSD, MG, and CIDP) [8,9,13]. While there is accumulating evidence of the efficacy of rituximab, safety data, especially in pediatric patients, have been relatively scarce, except for one large cohort study, which reported a variety of adverse events related to rituximab including fever, chills, skin rash, headache, tachycardia, anemia, thrombocytopenia, and neutropenia [14]. We performed the present study to investigate the efficacy and safety of rituximab for pediatric autoimmune neuroinflammatory disorders.

Methods and Methods

1. Study population

We collected a list of patients who received rituximab treatment at Seoul National University Children’s Hospital between January 1, 2009 and December 31, 2018. From these 104 patients treated with rituximab, we selected 32 patients with autoimmune neuroinflammatory disorders including anti-NMDAR encephalitis, OMAS, other suspected autoimmune encephalitis, NMOSD, and CIDP. The definition of each subgroup is provided in Supplementary Table 1 [15-18]. This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB no. H-1911-201-1086). Written informed consents from patients were waived due to a retrospective nature of the study.

2. Analysis of clinical variables and laboratory data

Clinical variables (demographic data, age at onset, diagnosis, first-line treatment, age at rituximab administration, and intensive care unit admission) were collected from the medical records. The complete blood count was analyzed to evaluate hematologic adverse events.

3. Rituximab treatment protocol

All patients received first-line treatment including corticosteroid, intravenous immunoglobulin (IVIG), or plasmapheresis. The dose and treatment duration of each first-line immunotherapy are listed in Supplementary Table 2. Rituximab was administered to patients who showed a refractory (NMDAR encephalitis, OMAS, and other suspected encephalitis) or recurrent clinical course (NMOSD and CIDP) after first-line immunotherapy. The treatment protocol consisted of 4 weekly rituximab infusions over 1 month. The dose of rituximab at each infusion was 375 mg/m² (maximum 500 mg).

All patients received prophylactic medications 30 minutes before rituximab infusion: oral acetaminophen (10 mg/kg), intravenous pheniramine (0.1 mg/kg, maximum 4 mg), and intravenous hydrocortisone (4 mg/kg, maximum 100 mg). The CD19+ cell count was measured before and after the four rituximab infusions. The decision whether to add additional rituximab infusion after one cycle of treatment was made on a clinical basis.

4. Analysis of efficacy outcome and safety

Clinical status was assessed using modified Rankin Scale (mRS) scores at the initiation of rituximab therapy and at last follow-up. Favorable clinical response parameters were defined as achievement of a mRS score ≤ 2 points, or an improvement of ≥ 2 points in mRS score at 2 months after initiation of rituximab and at the last follow-up [8,14,19,20].

Acute infusion-related adverse events were defined as unexpected and unfavorable responses that developed during the infusion of rituximab. Infectious adverse events were defined as complications that were related to immunosuppression after rituximab infusion. All management of adverse reactions was recorded. All adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE v. 5.0) [14].

Results

A total of 32 patients were included in the analysis. The median age at disease onset was 8.5 years (range, 1.1 to 17.1). The duration of follow-up after rituximab administration was a median 2.1 years (range, 0.2 to 8.1).

The demographic data of the patients and their disease subgroups are summarized in Table 1. First-line treatment with methylprednisolone was administered to 34 (97.1%), IVIG to 32 (91.4%), and plasmapheresis to seven patients (20%).

The median age at initiation of rituximab therapy was 9.0 years (range, 1.6 to 19.8) and the median duration of disease before rit-
Rituximab therapy was 0.3 years (range, 0.03 to 8.05). The median number of additional rituximab infusions after the initial 4 weekly infusions was 1 (range, 0 to 7). The variety of the time to rituximab therapy and the number of additional therapy after one cycle according to disease subgroup is presented in Table 2.

1. Efficacy outcome

Five of 32 patients (15.6%) were admitted to the intensive care unit at initiation of rituximab therapy. The median mRS scores were 5 (range, 4 to 5) at initiation, 2 (range, 1 to 5) at 2 months, and 1 (range, 0 to 3) at last follow-up. A favorable outcome was demonstrated in six patients (54.6%) at 2 months and 10 patients (91%) at last follow-up. In the OMAS group, the median mRS score was 3 (range, 3 to 4) at initiation, 1 (range, 1 to 2) at 2 months, and 0 (range, 0 to 1) at last follow-up. A favorable outcome was demonstrated in all 10 OMAS patients (100%) at 2 months and at last follow-up. NMOSD patients showed not only an improvement in neurological function, but also a decrease in the annual relapse rate from 2.5 per year (range, 2 to 3) to 0.5 per year (range, 0 to 1). Two patients with anti-NMDAR encephalitis and three patients with other suspected autoimmune encephalitis showed refractory clinical courses despite additional rituximab therapy, and they received other immunotherapies including cyclophosphamide and tocilizumab (data not shown).

All 32 patients showed the decrease of B-cell count after one cycle of rituximab. Before rituximab treatment, the median CD19⁺ B-cell count was 617/μL (range, 45 to 2,213), and the median proportion of total CD19⁺ B-cells within the lymphocytes was 28% (range, 4% to 53%). After 4 weekly rituximab infusion, the median

<p>| Table 1. Demographic characteristics, age at disease onset, and first-line treatment according to disease subgroup |</p>
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NMDAR encephalitis (n = 11)</th>
<th>OMAS (n = 10)</th>
<th>Other suspected AE (n = 5)</th>
<th>NMOSD (n = 4)</th>
<th>CIDP (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female-to-male ratio</td>
<td>9:2</td>
<td>6:4</td>
<td>4:1</td>
<td>3:1</td>
<td>1:1</td>
</tr>
<tr>
<td>Age at onset (yr)</td>
<td>12.2</td>
<td>1.5</td>
<td>14.6</td>
<td>9.6</td>
<td>3.6</td>
</tr>
<tr>
<td>(1.8–17.1)</td>
<td>(1.1–8.5)</td>
<td>(11.2–16.5)</td>
<td>(8.2–11.8)</td>
<td>(1.6–5.6)</td>
<td></td>
</tr>
<tr>
<td>First-line immunotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid</td>
<td>11</td>
<td>10</td>
<td>5</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>IVIG</td>
<td>11</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>PE</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Values are presented as number or median (range).
NMDAR, N-methyl D-acetyl receptor; OMAS, opsoclonus-myoclonus ataxia syndrome; AE, autoimmune encephalitis; NMOSD, neuromyelitis optica spectrum disorder; CIDP, chronic inflammatory demyelinating polyneuropathy; IVIG, intravenous immunoglobulin; PE, plasma exchange.

| Table 2. Rituximab treatment–related clinical variables and outcomes |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Variable | NMDAR encephalitis | OMAS | Other suspected AE | NMOSD | CIDP |
| Disease duration before RTX (yr) | 0.1 | 0.9 | 0.2 | 2.5 | 1.0 |
| (0.03–0.34) | (0.42–2.22) | (0.09–0.33) | (0.27–8.05) | (-) |
| No. of additional RTX treatments | 1 | 0 | 3 | 1.5 | 0.5 |
| (0–7) | (0–2) | (0–4) | (0–5) | (0–1) |
| Follow-up duration after RTX (yr) | 2.0 | 4.1 | 1.8 | 1.6 | 4.1 |
| (0.2–4.5) | (1.7–7.0) | (0.9–3.5) | (0.6–8.1) | (3.5–4.7) |
| mRS score at initiation/at 2 months after initiation/at follow-up (median) | 5/2/1 | 3/1/0 | 4/4/2 | 4/3/2.5 | 4/3/2 |

Values are presented as median (range).
NMDAR, N-methyl D-acetyl receptor; OMAS, opsoclonus-myoclonus ataxia syndrome; AE, autoimmune encephalitis; NMOSD, neuromyelitis optica spectrum disorder; CIDP, chronic inflammatory demyelinating polyneuropathy; RTX, rituximab; mRS, modified Rankin Scale.
CD19+ B-cell count decreased 0/μL (range, 0 to 6.04), and the median proportion was 0% (range, 0% to 0.27%).

2. Adverse events

Infusion-related complications were reported in nine of 32 patients (28.1%) (Table 3). There was no difference in the frequency of adverse events among disease subgroups. No infectious complications related to rituximab, including progressive multifocal leukoencephalopathy, were reported in our study group. All complications were below grade 3 CTCAE. Most symptoms related to adverse events were temporary or recovered after the infusion rate was slowed and symptomatic treatment with antihistamine and antipyretics as administered. No adverse events resulted in the withdrawal of rituximab.

**Table 3. Infusion-related adverse events of rituximab**

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Total patients</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>9 (28.1)</td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td>5 (15.7)</td>
<td></td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>3 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (6.3)</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>2 (6.3)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td>1 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (6.3)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (3.1)</td>
<td></td>
</tr>
</tbody>
</table>
Discussion

The results of this single center, retrospective study support the efficacy and safety of rituximab in pediatric autoimmune neuroinflammatory disorders.

Many previous studies have evaluated the efficacy of rituximab in autoimmune diseases of the nervous system. Dale et al. [14] performed a multicenter retrospective study of 144 children and adolescents. They analyzed the increased proportion of patients with mRS scores \( \leq 2 \) at initiation of rituximab treatment and at last follow-up, and reported an improved outcome in 73.9% of patients at last follow-up. In another study, Fu et al. [21] also evaluated the efficacy of rituximab in 38 children and reported a good response in 74% of patients. Similarly, efficacy results in our study of 35 patients showed an improved outcome in 77.1% of patients at last follow-up. Hence, the overall efficacy of rituximab seen in our study is consistent with those seen in previous studies.

Several pediatric studies have explored the efficacy of rituximab in anti-NMDAR encephalitis, OMAS, and NMOSD. Our study results are also consistent with those of these previous studies. For anti-NMDAR encephalitis, a good outcome (mRS score 0 to 2) was reported in 78% and 90% of patients treated with rituximab at last follow-up [8,22]. We also demonstrated a comparable favorable outcome in 10 of 11 patients (91%) at a median 2 years follow-up. In patients with OMAS, an improved outcome (mRS score 0 to 2) was identified in 93.3% of patients at last follow-up [14]. Our study showed comparable favorable outcomes in 100% of patients at 2 months after initiation and at last follow-up. These results reflect the high efficacy of rituximab in refractory OMAS [23]. In NMOSD, a favorable outcome (mRS score 0 to 2) was reported in 90% of patients at last follow-up and there was a decrease in the annual relapse rate from 2.0 to 0.16 [14,24]. Although our study sample size was small, our data also showed a good outcome in two of four patients (50%) and also a decrease in the annual relapse rate (from 2.5 to 0.5). Considering both our study and those reported previously, the use of rituximab therapy in anti-NMDA encephalitis, OMAS, and NMOSD should be considered as soon as possible, and active use of rituximab is expected to improve the outcomes.

Although there were limited previous data about the effect of rituximab in patients with CIDP, the results in our study showed a promising trend. In patients with refractory CIDP, a previous study reported that two of three patients (66.6%) showed improvements in motor scale and morbidity [12]. Our study demonstrated a good outcome in one of two patients (50%) at both 2 months and at last follow-up. However, although we confirmed the consistently favorable outcomes, only a few small studies have explored rituximab in CIDP. Hence, further studies are needed to support the evidence for the efficacy of rituximab.

Previous studies reported rituximab infusion-related acute complications in 5% to 53% of patients with pediatric nephrotic syndrome [5,25,26]. In adult NMOSD, a systematic review and a meta-analysis reported infusion-related adverse events in 45 of 438 patients (10.3%) [27]. Infusion-related acute reactions were reported in 18 of 144 patients (12.5%) with pediatric autoimmune neuroinflammatory disorders [14]. Compared with this previous study, adverse events were observed in 10 of 35 patients (28.5%) in our study. This difference may be related to the method of classification of adverse events. The two previous studies did not include hematologic complications (anemia, thrombocytopenia, and neutropenia). If we exclude such hematologic complications, the adverse events rate decreases to 11.4% (four of 35 patients). The relatively smaller number of study patients might also magnify the results. Another small study of pediatric patients with central demyelinating disease showed infusion-related reactions in three of 11 patients (27.2%) [28]. Although we saw no difference between disease subgroups in the frequency of adverse reactions, it is necessary to consider this in the context of patients’ disease-related general condition. Nine patients with anti-NMDAR encephalitis and suspected autoimmune encephalitis developed fever with tachycardia before rituximab infusion, which continued during infusion. Because these events commenced before the infusion, we did not include them as infusion-related adverse events. Although there were some infusion reactions in our study, all adverse events were below grade 3 CTCAE and subsided after slowing of the infusion rate and administration of antipyretics. Overall, the data indicate that infusion-related adverse events of rituximab are well tolerated.

Previous studies have reported rituximab-related infectious adverse events including some serious infectious complications such as sepsis [14,26], Pneumocystis jiroveci pneumonia [21,29], hypogammaglobulinemia [14,30], and progressive multifocal leukoencephalopathy [29]. In one large pediatric cohort study, infectious complications occurred in 41 of 573 patients (7.3%) with autoimmune disease [29]. However, there were no infectious complications seen in our study. This result might be related to the small number of patients and relatively short follow-up period for evaluating infectious complications. It is also possible that patients might not have reported minor infectious events. Importantly, because previous studies have reported discontinuation of rituximab related to infectious adverse events, infectious complications should be monitored carefully during rituximab treatment and the acquisition of long-term safety data for rituximab in neuroinflammatory disease is required.

In our single center study, all patients received the same rituximab.
imab therapy protocol. Thus, our study data could provide powerful evidence for evaluating the efficacy and safety of rituximab. Our results have value in terms of the evidence supporting the efficacy and safety of rituximab treatment in pediatric autoimmune neuroinflammatory disorders. The accumulated data suggest that rituximab can be administered actively and we expect that rituximab will be of benefit in a range of neuroinflammatory diseases [31].

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.26815/acn.2019.00290.

Conflicts of interest

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

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References

Orolingual tremor is a rhythmic, involuntary movement of the jaw, tongue, pharynx, or lower face [1]. It is often described in Parkinson’s disease and can be seen in patients with severe essential tremor. Some medications, especially neuroleptics, have been reported to cause orolingual tremors. Orolingual tremors can be classified as resting tremors or activation-induced tremors. Activation-induced tremors include positional and task-specific tremors. Task-specific tremors are defined as no tremor at rest, but occurs exclusively during a specific task including speaking, whistling, smiling, or playing wind instruments. Task-specific orolingual tremors induced by smiling is a rare phenomenon. So far, only two adult case series of facial tremor occurring on smiling have been described in the literature [2,3]. Orolingual tremor on smiling in children has not been reported yet. We report a child who present with orolingual tremor only on smiling due to activation of the risorius muscles.

This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB No. B-1905-540-701). Informed consent was waived by the board. A 16-year-old boy was referred with orolingual tremor induced by smiling. He had this symptom for few years. Recently, the frequency of tremor increased and his friends often mentioned about his facial tremor. He previously had a prolonged course of topical steroid therapy prescribed for atopic dermatitis. He has not exposed to any neuroleptics prior to the onset of tremor. There was no postural limb tremor, no family history. On neurologic examination, orolingual tremor was not detected at rest. Saying ‘a,’ ‘e,’ or tongue protrusion did not induce tremor. Bilateral arrhythmic tremor around the lip was induced exclusively on smiling. The reminder of his neurologic examination was normal. A brain magnetic resonance imaging excluded any brain parenchymal pathology. All blood tests including complete blood count, chemistry, electrolytes, thyroid function test, magnesium, ionized calcium were normal. We performed needle electromyogram (EMG) recording from the orbicularis orii and risorius muscles. Needle EMG activity was recorded at rest and smiling. Patient had normal EMG recording at rest without myokymic discharges. EMG during smiling revealed approximately 9 to 10 Hz bursts of 76 ms duration in the risorius muscles associated with visible bilateral tremors (Fig. 1). His tremor on smiling did not responded to propranolol.

We described a child with orolingual tremor exclusively induced by smiling due to activation of the risorius muscles. This child had no evidence of orolingual dystonia, essential tremor, or associated neurological disorders. This tremor on smiling is a rare disease entity. It did not occur at rest, nor associated with dystonia. This is one of the task-specific orolingual tremors which oc-
cur exclusively during specific postures or tasks. Task-specific orolingual tremor induced by drinking or by positioning one’s teeth close together have been reported [4]. Jacome and Yanez [2] described the first case of a 27-year-old woman who presented with perioral facial tremor induced by smiling. She had no underlying neurologic disease, but family history of facial tremor. Hence, facial tremor was suggested as a form of familial essential tremor. Furthermore, Schwingenschuh et al. [3] described two adult cases with orolingual tremor induced by smiling. One patient had young-onset Parkinson’s disease, whereas the other had no neurological disorders. Orolingual tremor had a frequency of 9 Hz and EMG burst duration were 70 to 85 ms. Our case also has a similar tremor peak frequency of 9 to 10 Hz and burst duration of 76 ms. Only smiling due to the activation of risorius muscles induced bilateral irregular arrhythmic tremor around the lip. Cause of tremor on smiling is uncertain, but it may be a discrete entity rather than a form of familial essential tremor or an early symptom of Parkinson’s disease. The incidence of task-specific orolingual tremor is low in children, but should be recognized and described by physician.

Conflicts of interest

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Fig. 1. The power spectrum analysis of the risorius muscles showed a peak at a frequency of 9 to 10 Hz.
Guillain-Barré syndrome (GBS) is an acute inflammatory demyelinating polyneuropathy, usually presenting with proximal muscle weakness of the lower extremities and sensory dysesthesia, commonly triggered by preceding viral or bacterial infections. Cranial nerve involvement has been reported in 45% to 75% of patients with GBS, facial nerve involvement being the most common [1]. Facial palsy in GBS is often bilateral. Unilateral facial palsy is rare, and very few cases have been reported [2,3]. There are a limited number of pediatric GBS cases with unilateral facial palsy described in the literature [4]. To date, there has been one pediatric case report with unilateral facial palsy as an isolated and presenting feature of GBS [5]. Here we report the case of an infant with GBS whose first presentation was unilateral peripheral facial palsy following gastroenteritis.

An 8-month-old boy visited our clinic complaining of left facial palsy. He could not close his left eye completely and showed drooping of his left lip. He had a history of bloody diarrhea three weeks before the visit. His medical history revealed secundum atrial septal defect and ventricular septal defect, for which he is being followed up at the cardiology clinic. On physical examination, his vital signs were as follows: heart rate of 100 beats per minute, blood pressure of 95/48 mm Hg, body temperature of 36.5°C. His motor power was Medical Research Council (MRC) grade 5 in all extremities, tone was normal, and deep tendon reflexes (DTRs) were normoreflexic in the biceps, knee, and ankle jerks. No pathological reflexes were present. Routine laboratory blood tests showed a normal complete blood count including the differential, and normal renal and liver function. Serum immunoglobulin M antibodies to Epstein-Barr virus, herpes simplex virus, and mycoplasma were negative. Stool tests for leukocyte, blood, and culture were negative. Stool polymerase chain reaction for Clostridium difficile toxin B and Clostridium perfringens were positive. The patient was diagnosed with idiopathic peripheral facial palsy. He was started on oral steroids. His facial palsy improved, and he was able to close his eyes while sleeping. However, on the 5th day after onset, he developed motor weakness in his legs. His motor strength was MRC grade 3 in the upper extremities and 1 in the lower extremities. DTRs were absent in the biceps, knee, and ankle jerks bilaterally. Cerebrospinal fluid analysis showed 1 white blood cell/µL with a protein level of 40.2 mg/dL. Antibodies to disialoganglioside (GD1b) and monosialoganglioside (GM1) were negative. Brain magnetic resonance imaging was unremarkable. GBS was diagnosed based on the clinical features, and a 5-day course of intravenous immunoglobulin was started from the day of onset of the motor
weakness. On the 6th day, he was reported to have poor sucking ability with a gurgling sound when feeding, and also reduced facial muscle expressions bilaterally. Nerve conduction study was performed on the 8th day after symptom onset. Sensory responses of both upper and lower limb nerves were normal. Motor responses of the left median and ulnar nerve showed a conduction block consistent with a demyelinating neuropathy (Fig. 1). From the 8th day, he was able to move his toes, and swallowing improved. Since then, his neurological condition gradually improved. On the 13th day, he could close both eyes while sleeping. He was discharged with rehabilitative treatment. On the 23rd day, his motor power recovered to MRC grade 5. On the 65th day, DTRs were elicited in the biceps and knee jerks. During the 2-year follow-up, he remained healthy without any neurologic sequelae.

The possible mechanism for facial palsy in GBS is thought to be secondary to the direct attack of antibodies, either causing demyelination or axonal degeneration, depending on the type of antibody involved. Hypertension may contribute to facial paralysis; edema or hemorrhage within the facial canal could cause neural compression [2].

Our case herein showed a very unique presentation of GBS. As mentioned before, unilateral facial palsy in GBS is rare, especially in children. Only a few pediatric case reports have been published [3-5]. Facial palsy in GBS usually follows limb weakness or at least presents simultaneously with other clinical features of GBS such as limb weakness, dysesthesia, and multiple cranial palsies. Presentation of facial palsy alone as the first symptom of GBS is rare [2-4]. There has been one case report of an 11-year-old girl presenting with unilateral facial palsy preceding motor weakness by three days, which is similar to our case [5]. Our patient developed bilateral incomplete facial palsy with bulbar palsy while unilateral facial palsy was improving, which showed a different clinical course from the previous pediatric cases [2-5]. He had no autonomic dysregulations such as labile hypertension, implicating his facial palsy not being related to hypertension.

Anti-GM2 with previous Campylobacter jejuni infection has been linked to bilateral facial paralysis. Iqbal et al. [3] reported a case of an adolescent girl with GBS who presented with unilateral facial palsy after C. jejuni infection, who was positive for anti GM1 and GM2 antibodies. Although our patient’s stool was positive for C. difficile toxin B and C. perfringens, we could not be certain about the relationship between unilateral facial palsy and the pathogens isolated from the stool. We could not check for anti GM2 antibodies either, which might have given more clues regarding the development of unilateral facial palsy with GBS in this infant.

The facial palsy reported with GBS is usually bilateral. However, it can rarely present unilaterally, which could be misdiagnosed as Bell palsy. Therefore, pediatricians should know about the associa-

![Motor NCS left median-APB](https://doi.org/10.26815/acn.2019.00255)

![Motor NCS left ulnar-ADM](https://doi.org/10.26815/acn.2019.00255)

**Fig. 1.** Motor responses of the left median (A) and ulnar (B) nerve show a conduction block consistent with a demyelinating neuropathy on nerve conduction study (NCS). APB, adductor pollicis brevis; ADM, abductor digiti minimi; TL, terminal latency; W-E, wrist-elbow; E-AX, elbow-axillary.
tion between unilateral facial paralysis and GBS. Written informed consent by the patients was waived due to a retrospective nature of our study.

Conflicts of interest

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

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References

Instructions to authors

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b. Once a case has been published in an original paper, it may not be reproduced as a case report. However, only in circumstances in which a novel diagnostic method, a novel therapeutic trial, or a previously unknown accompanying condition is found will the editorial board determine the possibility of acceptance.

c. Clinical trials on drugs with commercial implications will be reviewed by the proper subcommittee or subspecialty before being reviewed for publication.

d. Clinical letters of previously published cases will not be accepted. The editorial board will make an exception only if the case is very rare. The *Annals of Child Neurology* index should be reviewed before the submission of clinical letters.

e. Rejected manuscripts may not be resubmitted.

f. The manuscript will be rejected if the author does not address the comments made by the reviewer or the manuscript does not follow the required guidelines.

**Manuscript preparation**

1. **General principles**

1) *Annals of Child Neurology* publishes original articles, reviews, letters to the editor, and editorials.

2) The manuscript should not have been published previously, and not have been submitted for publication elsewhere. Any conflicts of interest of all listed authors should be stated.

3) The manuscript should be written according to the prescribed format. If not, the editorial board may return it before reviewing. The editorial board decides on publication and may modify a portion of the text with little effect on the original.

4) The manuscript must be written in English. Authors (particularly non-native English speakers) who submit the original article or letters to editor should check their manuscript by using professional editing service and submit the manuscript with a certificate of English review, including the name, institution, position, statement of approval, and signature with unstructured format.

5) The text of the manuscript, including tables and their footnotes and figure legends, must be double-spaced and in standard 12-point font on A4 paper size with left and right margin spaces of 2 cm and top and bottom margins of 3 cm.

6) Except for units of measurement, abbreviations are strongly discouraged. Do not use abbreviations in the title or abstract and limit their use in the text. Expand all abbreviations at first mention in the text.

7) Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) and laboratory values should be displayed in International System of Units (SI).

8) The number of pages of manuscripts of reviews and original articles has no limitation but no more than 10 printed pages are recommended. Letters to editor should be written in a maximum of 2 printed pages.

2. **Cover letter**

The cover letter accompanying the manuscript must specify the type of manuscript and include statements on ethical issues and conflicts of interest, and complete contact information for the corresponding author.

The cover letter should include the following statement: “All authors have read and approved the submitted manuscript, the manuscript has not been submitted elsewhere nor published elsewhere in whole or in part, except as an abstract (if relevant).” The cover letter may include the names of up to 3 potential reviewers whom the authors would like to suggest, especially members of the editorial board. The authors may also include the names of up to 3 reviewers whom they would like not to evaluate their submission. The editor ultimately decides who will review the manuscript.

3. **Original articles**

Original articles are papers reporting the results of basic or clinical investigations, which are sufficiently well documented to be acceptable to critical readers. The manuscript should be prepared according to Recommendations from ICMJE. The manuscript should have the following sequence: Title page, Abstract and Keywords, Introduction, Materials and Methods, Results, Discussion, Acknowledgment, References, Tables, and Figure Legends. All pages should be numbered consecutively in the middle of the bottom margin, starting with the title page.

**Title page**

The title page should contain the following information: (1) title; (2) author list (full names of authors); (3) name of the institutions...
at which the work was performed; (4) acknowledgement of research support; (5) name, address, telephone, fax number, and e-mail address of the corresponding author; (6) a running title should be written of 10 words or less.

Abstract and keywords
The abstract should be a single paragraph of less than 250 words, and describe concisely, the purpose, methods, results, and conclusion of the study, in a structured format. Abbreviations, if needed, should be kept to an absolute minimum, and their first use should be preceded by the full term in words. The abstract should not include footnotes, references, or tables. The abstract can be modified by an English language reviewer who is appointed by the editorial board. A maximum of 5 keywords should be listed at the end of the abstract to be used as index terms. For the selection of keywords, refer to Medical Subject Headings (MeSH; https://meshb.nlm.nih.gov/search).

Introduction
The introduction should provide the background of the study and state the specific purpose of research or hypothesis tested by the study. It may mention previous publications most closely related to the article.

Materials and Methods
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.

Discussion
Observations pertaining to the results of research and other related materials should be interpreted for your readers. Emphasize new and important observations; do not merely repeat the contents of the results. Explain the meaning of the observed opinion along with its limits, and within the limits of the research results connect the conclusion to the purpose of the research. In a concluding paragraph, summarize the result and its meaning.

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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Open researcher and contributor IDs (ORCID) are recommended for authors. To receive ORCID, authors should register on the ORCID website available from: https://orcid.org.

References
Reference citations in the text should be made with consecutive numbers in parenthesis (Vancouver style). References should be listed in the order of citation in the text, with the corresponding number. The reference style for journal articles is as follows: names of authors, full title of article, journal name abbreviated in accordance with MEDLINE, year, volume, and page numbers. List all authors when they are six or less; when they are seven or more, list the first six and add ‘et al.’ The names of all authors must be listed by the last name and the initials of the first and middle names. Papers in press may be listed with the journal name and tentative year of publication. The style for a chapter of a book is as follows: author and title of the chapter, editor of the book, title of the book, edition, volume, place, publisher, year, and page numbers. Cite unpublished data or personal communications in the text only and not in the reference list. Internet URLs should be as follows; authors’ names, website title, URL and the time of
the latest update. All other references should be listed as shown in the Recommendations from ICMJE. Authors are responsible for the accuracy and completeness of their references. The maximum number of cited references should be 40 for original articles and 5 for letters to editor.

Examples of reference styles

1) Journal article

2) Book
- Book
- Book chapter
- Abstract book or conference proceedings
- Thesis

3) Website

Tables
1) Each table should be inserted on a separate page, with the table number, table title and legend.
2) The numbers of tables should be in Arabic numerals in their order of citation.
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.
5) The significance of results should be indicated by appropriate statistical analysis.
6) Unnecessary longitudinal lines should not be drawn. Horizontal lines should be used as sparingly as possible.
7) All symbols and abbreviations should be described below the table.
8) Use superscript letters (a, b, c) to mark each footnote and be sure each footnote in the table has a corresponding note. List abbreviations in the footnote section and explain any empty cells.
9) All units of measurements and concentrations should be designated.

Figures and figure legends
1) Figures should be submitted separately from the text the manuscript. All pictures and photographs should be of excellent quality and supplied as JPEG or TIFF files with resolution of more than 300 dpi. The preferred size of figure is 7.4×10.0 cm (3×4 inches). Except for particularly complicated drawings that show large amounts of data, all figures are published at one page or one column width. All kinds of figures may be reduced, enlarged, or trimmed for publication by the editor.
2) Color figures and pictures will be published if the editor decides it is absolutely necessary.
3) Figure numbers, in Arabic numerals, should appear in the figure legends. Arabic numerals should be used in the order in which the figures are referred to in the main text. In cases where more than two photographs are used with the same number, alphabet characters should be used next to the Arabic numeral (e.g.: Fig. 1A, Fig. 1B).
4) All pictures and photographs should be described in the legend with complete sentences rather than incomplete phrases or a clause.
5) All symbols and abbreviations should be described below the figure.
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All other types of manuscripts should meet the above mentioned requirements.

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Reviews may be written by invitation by the editorial board and provide concise reviews of important subjects to medical researchers. They are organized as follows: title page, abstract and keywords, introduction, main text, conclusion, acknowledgments, references, tables, figure legends, and figures. An abstract is required but it need not be structured. Reviews should not exceed 7,000 words, include no more than 6 figures or tables and 150 references.

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Letters to Editor is a type of brief communication on any topics that attract attention of journal readers. It should be brief, clear and conclusive. No abstraction is required. Body of the letter has no structure and the word count is limited to 1,000 words. It should be written in a maximum of 2 printed pages, less than 5 references, less than 2 table or figures, and less than 5 authors.

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Manuscripts accepted for publication

1. Final version

After the paper has been accepted for publication, the author(s) should submit the final version of the manuscript. The names and affiliations of the authors should be double-checked and if the originally submitted image files were of poor resolution, higher resolution image files should be submitted at this time. The EPS, JPG, PPT, or TIF formats are the preferred digital files for photographic images. Symbols (e.g., circles, triangles, squares), letters (e.g., words, abbreviations), and numbers should be large enough to be legible even after on reduction to the journal’s column widths. All symbols must be defined in the figure captions. If references, tables, or figures are moved, added, or deleted during the revision process, renumber them to reflect the changes so that all tables, references, and figures are cited in numeric order.

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Before publication, the manuscript editor will correct the manuscript such that it meets the standard publication format. The author(s) must respond within 7 days when the manuscript editor contacts the author for revisions. If the response is delayed, the manuscript’s publication may be postponed to the next issue. The author should double-check for corrections in the content, title, affiliation, capitalization, locations of figures, and references. Corresponding authors are responsible for further corrections made after printing.

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The author(s) will receive the final version of the manuscript as a PDF file. Upon receipt, within 2 days, the editorial office (or printing office) must be notified of any errors found in the file. Any errors found after this time are the responsibility of the author(s) and will have to be corrected as an erratum.

4. Feedback after publication

If the authors or readers find any errors, or contents that should be revised, it can be requested from the Editorial Board. The Editorial Board may consider erratum, corrigendum or a retraction. If there are any revisions to the article, there will be a CrossMark description to announce the final draft. If there is a reader’s opinion on the published article with the form of Letters to the editor, it will be forwarded to the authors. The authors can reply to the reader’s letter. Letters to the editor and the author’s reply may be also published.

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The policy of Annals of Child Neurology is primarily aimed at protecting the authors, reviewers, editors, and the publisher of the journal. If not described below, the process of handling complaints and appeals follows the guidelines of the Committee of Publication Ethics available from: https://publicationethics.org/appeals.

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Who is responsible to resolve and handle complaints and appeals?
The Editor, Editorial Board, or Editorial Office is responsible for them. A legal consultant or ethics editor may be able to help with the decision making.

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It depends on the type or degree of misconduct. The consequence of resolution will follow the guidelines of the Committee of Publication Ethics (COPE).

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Once the manuscript is at the publisher, confirmation of acceptance by the Annals of Child Neurology may be issued.

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All accepted manuscripts are subject to copyediting. Before publication, page proofs are sent to the corresponding author, who is responsible for verifying the final manuscript contents, including all copyediting changes. Once a manuscript has been typeset, copyedited, and approved by the editor and the authors, it will soon appear online in our "Ahead-of-Print" section.

Further information
Any correspondence, queries or additional requests for information on the manuscript submission process should be sent to Annals of Child Neurology editorial office as follows:
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E-mail: editor@annchilneurol.org
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Author's checklist

1. General provisions
☐ The authors should ensure that the contents of the present manuscript have not been published nor intended to be published in other journals.
☐ The manuscript should be formatted as follows: A4 paper, 12 point font, left-aligned, double-spaced.
☐ An original article should be presented in the following order: cover page, abstract, keywords, introduction, methods, results, discussion, references, and captions and legends for tables and figures.

2. Cover page
☐ This section should indicate the contact information of the corresponding author: postal code, address, phone number, fax number, and email address.
☐ A running title should be given in 10 words or less.

3. Abstract and Keywords
☐ The abstract should be divided into Background and Purpose, Methods, Results, and Conclusions; it should be written in one paragraph that is within 250 words.
☐ Three to six keywords should be included (preferably those recommended in MeSH of Index Medicus; the first letter of each key word should be capitalized).

4. Main text
☐ The title should not include abbreviations; all the words must be spelled out.
☐ Information regarding approval of an institutional review board and obtaining informed consent should be mentioned in the Method section.
☐ References should be numbered in Arabic numbers in the order they are cited.
☐ Superscript numbers should come after commas and periods according to submission rules.
☐ When using abbreviations, their full forms should be used at first mention; abbreviations/acronyms should then be used consistently in further occurrences.
☐ Units of measure should be written in accordance with submission rules (except for % and °C, a space should come between the number and the unit of measure).
☐ For numbers, a comma should be inserted after every third digit.
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5. References
☐ In-text citations should be numbered and should correspond to the numbers in the references.
☐ Up to six authors should be mentioned. In case there are seven or more authors, “et al.” must come after the primary author.
☐ Official abbreviations of quoted journals must be used.
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☐ The first letter of the title of the quoted article should be capitalized.
☐ Compliance with quotation styles should be observed.
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6. Table
☐ Each table must have its own title and be given a separate page.
☐ All abbreviations used in the table should be spelled out.
☐ All superscript numbers used in the table should comply with the contribution rules.

7. Figures
☐ Each figure should be produced in a separate file and should not be included in the main text.
☐ The file name of each figure should be the figure number.
☐ Figures can be black and white or in color; they will be published as submitted.
☐ The titles and legends of the figures should be concisely drafted on a separate page in English.
☐ The figures should be explained in complete sentences, not phrases or clauses.
☐ All abbreviations should be written out.
☐ When a figure contains several pictures, the explanation of the figure should be followed by that of each picture, distinguishing them as A, B, C, etc.
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1. 경고  
1) 발진 : 이 약의 투여와 관련하여 특히 소아에서, 잠재적으로 생명을 위협하는 중증의 피부발진(스티븐스-존슨 증후군, 독성표피괴사용해 포함)이 보고된 바 있다.  
2) 혈구탐식성 림프조직구증(HLH; hemophagocytic lymphohistiocytosis): 이 약을 복용중인 환자에서 HLH가 발생하였다. 이것의 증후나 증상이 나타난 환자는 즉시 평가하여야 하며, HLH 진단검사를 고려해야 한다.  

2. 다음 환자에는 투여하지 말 것  
1) 간질(뇌전증)  
1) 단독 및 부가요법 : 부분발작 및 전신 강직간대발작  
2) 부가요법 : 레녹스-가스토 증후군에 의한 발작  
2) 양극성 1형 장애 환자에서의 우울삽화의 재발 방지  

3. 다른 항전간제에 대한 과민반응 또는 발진의 병력이 있는 환자  
4) 임부 또는 임신하고 있을 가능성이 있는 여성, 임신을 원하는 여성  
5) 수유부  
6) 심전도 이상이 있거나 방실 전도 억제 약물이 투여중인 환자

7. 수유부에 대한 투여  
수유의 잠재적 유익성은 신생아에서 나타날 수 있는 유해반응의 잠재적 위험성을 상회하여야 한다. 이 약 투여 시 수유하지 않는다.  

8. 피임제의 유효성에 미치는 영향  
생식 활동을 하고 있으며, 특별한 피임법을 사용하지 않는 여성 환자에서는 임상시험에서의 호르몬적 변화로 인한 임신 가능성이 확인되었다고 판단되는 후기 시험단계의 임상시험을 통해, 이 약물이 임신에 영향을 미치는 것을 나타낸 적이 있었다.  

9. 신중투여  
수입의약품

10. 용법·용량 :  

11. Safety information:  

12. Abbreviated Prescribing Infomation Version 07

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## Topiramate 서방형 제제

### 국내 최초의 Topiramate 서방형 제제.

### 복약편의성을 개선한 Topiramate 서방행 제제.

### FDA 허가를 받은 Topiramate 서방행 제제.

### 25mg

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### Refrences

3. Qudexy XR. FDA Prescribing Information(revised 02/2018, Reference ID: 4075003)

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**1. 간질(뇌전증)**

1. 단독 및 부가요법: 부분발작 및 전신 강직간대발작
2. 부가요법: 레녹스-가스토 증후군에 의한 발작

**2. 양극성 1형 장애 환자에서의 우울삽화의 재발 방지**

**3. 임부에 대한 투여**

4. 이상반응

5. 일반적 주의

6. 임부에 대한 투여
High Dose I.V.-Globulin SN inj. 10%

- First High Dose immunoglobulin in Korea
- High Volume IVIG
- Reduced Infusion time
- Reduced Volume load
소아 플로jack, 후기 발병형 폴페병

만약 아이가 달리거나 운동하는데
어려움을 느끼는 등의 근육약화가 있다면,

폴페병 검사를 서둘러 주세요.

폴페병은 치료 가능한 질환입니다. 3-5
조기 진단과 치료는 특히
운동기능과 호흡기능 결과를 개선시킬 수 있습니다. 3-6
Synergistic Seizure Control

Simple, Once-daily
Exegran® and Perampanel is a 1-10 mg dose that may be effective in all patients with epilepsy.

Synergism of Zonisamide & Perampanel
In vivo experiments showed Zonisamide and Perampanel combination was effective in reducing seizure frequency. The combination of Zonisamide and Perampanel was studied in a variety of experimental models, including the kindling model and the Pentylenetetrazol (PTZ) model.

Greater effectiveness and lower risks
Exegran's Broad Spectrum action is ideal for patients who require a combination therapy. Perampanel's Unique action is a good choice for patients who are already on standard antiepileptic medications.

References