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, neurogenetics, neuromaging, neuromuscular medicine, immunomunology 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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Clinical Characteristics of Epilepsy and Its Risk Factors in Neurofibromatosis Type 1: A Single-Center Study

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Purpose: This study investigated the clinical characteristics and risk factors of epilepsy in patients with neurofibromatosis type 1 (NF1) at a tertiary center.

Methods: The medical records of 103 children diagnosed with NF1 from February 2009 to July 2019 were retrospectively reviewed. Demographic features, NF1-related features, seizure characteristics, treatment outcomes, and electroencephalography and brain magnetic resonance imaging (MRI) findings were compared between patients with and without epilepsy.

Results: Among the 103 patients (median age, 11.5 years; age range, 1.0 to 34.8), 14 (13.6%) had epilepsy. The median age of seizure onset was 5.8 years (range, 1.1 to 18.9). Focal and generalized seizures were observed in nine (64.3%) and six (42.9%) patients, respectively. Five patients (35.7%) had a history of status epilepticus and one of them died of it. Two patients (14.3%) had drug-resistant epilepsy. On brain MRI obtained at the time of seizure onset, seven (50%) patients had unidentified bright objects and three (21.4%) had other structural abnormalities. Learning disability (odds ratio [OR], 4.5; 95% confidence interval [CI], 1.17 to 17.5) and a family history of epilepsy (OR, 39.7; 95% CI, 3.78 to 416.53), but not structural abnormalities, were significant risk factors for epilepsy.

Conclusion: Epilepsy was more common in NF1 patients than in the general population. NF1 patients with epilepsy had various seizure types, but exhibited relatively good outcomes. The types of brain abnormalities were not significantly different between patients with and without epilepsy. Our results suggest that mechanisms other than structural brain abnormalities should be considered epileptogenic in NF1 patients.

Keywords: Neurofibromatosis 1; Epilepsy; Learning disabilities; Risk factors

Introduction

Neurofibromatosis type 1 (NF1) is one of the most common neurocutaneous disorders with a prevalence of approximately from 1/2,000 to 1/5,000 in most population-based studies [1]. It is an autosomal dominant genetic disorder caused by mutation of the NF1 gene, which encodes neurofibromin—tumor suppressor protein that inhibits intracellular Ras signaling [2]. Neurofibromin is highly expressed within the cerebral cortex during embryologic development and it may play an important role in neurodevelopment [3,4]. Hence, patients with NF1 present with not only typical characteristic signs of NF1 such as café au lait spots, Lisch nod-
ules, axillary or inguinal freckling, neurofibromas, distinctive osseous lesions, and optic gliomas, but also with neurologic symptoms, such as learning disability, behavioral problems, attention deficit, headache, and epilepsy.

The prevalence of epilepsy in patients with NF1 is reportedly 4% to 13%, higher than the general population (0.45% to 1%) [5-8]. Although this epilepsy predisposition was first postulated more than 30 years ago, the underlying mechanism has not been fully elucidated [9]. Several studies have described factors associated with epilepsy in NF1, but no consistent patterns have yet emerged [5,6,8,10-12]. This study aimed to analyze the clinical features and risk factors of epilepsy in patients with NF1 at a single tertiary center.

Materials and Methods

We retrospectively reviewed the medical records of all patients diagnosed with NF1 at Kyungpook National University Hospital from February 2009 to July 2019. All patients fulfilled the National Institutes of Health diagnostic criteria for NF1 [13]. We collected the following data from the patients with epilepsy: age of seizure onset, seizure semiology and frequency, number of anti-epileptic drug (AED) medications, family history of epilepsy, and electroencephalography (EEG) findings. Patients who had not visited the hospital for the past year were interviewed via telephone for data collection. Epilepsy was defined and classified according to the International League Against Epilepsy classification [14-16]. Patients with febrile seizures were excluded. Drug-resistant epilepsy (DRE) was defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules to achieve sustained seizure freedom [17].

Clinical characteristics, including demographic features, family history, NF1-related features, learning disability, and brain magnetic resonance imaging (MRI) findings, were compared between patients with and without epilepsy to identify epilepsy risk factors. Learning disability was determined based on neuropsychiatric testing and parental interviews. Neuroimaging findings were reviewed by an experienced neuroradiologist blinded to patient information. Brain MRI findings closest to the time of seizure onset in patients with epilepsy were compared with the latest MRI findings in patients without epilepsy. This study was approved by the Institutional Review Board of the Kyungpook National University Hospital (IRB file no. 2020-06-050). Written informed consent by the patients was waived due to a retrospective nature of our study.

Demographic data are presented as proportions or medians. Clinical characteristics between the patients with and without epilepsy were analyzed using the two-tailed Fisher’s exact test or chi-square test for categorical variables and the Mann–Whitney U test for continuous variables. To identify epilepsy risk factors in NF1, multiple logistic regression model with a backward stepwise approach was used. Analysis results are presented using odds ratios (ORs) with 95% confidence interval (CI). P < 0.05 was considered statistically significant.

Results

1. Patient characteristics

The study included 103 patients (52 female, 51 male) for analysis. Median patient age was 11.5 years (range, 1.0 to 34.8). Median age at diagnosis and follow-up duration were 4.5 years (range, 0.1 to 20.5) and 73.0 months (0.5 to 282.4), respectively. Among them, 14 patients (13.6%, three females) had epilepsy. Median age at diagnosis and follow-up duration of the patients with epilepsy were 5.4 years (range, 0.4 to 11.0) and 76.8 months (range, 12.4 to 211.3), respectively. Seven patients (50%) had a family history of NF1, two of whom inherited it from their affected mothers. Nine patients (64.3%) had a learning disability. Five patients (35.7%) had a family history of epilepsy; two had affected siblings. Characteristic signs and symptoms of NF1 were present as follows: café au lait spots (n = 14), axillary or inguinal freckling (n = 8), neurofibromas (n = 3), Lisch nodules (n = 7), scoliosis (n = 2), and skeletal dysplasia (n = 1). MRI findings at seizure onset were normal in six patients (42.9%) and unidentified bright objects (UBOs) in seven (50%). Three patients showed structural abnormalities except UBOs, including moyamoya syndrome (n = 1), subdural hematoma (n = 1), and Chiari malformation type 1 (n = 1). No brain tumor was observed. Table 1 shows the comparison of clinical characteristics between the patients with and without epilepsy. The epilepsy group had a significantly higher proportion of patients with learning disability (P = 0.005) and family history of epilepsy (P < 0.001). Structural brain abnormalities in MRI were not different between the two groups.

2. Epilepsy in neurofibromatosis type 1

Table 2 shows the epilepsy characteristics of the patients with epilepsy. In these 14 patients, median age of seizure onset was 5.8 years (range, 1.1 to 18.9). Nine (64.3%) had focal seizures (focal impaired awareness motor seizure, n = 4; behavioral arrest, n = 2; focal aware motor seizure, n = 2; focal to bilateral tonic-clonic seizure, n = 3), six (42.9%) had generalized seizures (absence seizure, n = 1; generalized atonic seizure, n = 1; generalized tonic seizure, n = 4), and one had unknown seizure (epileptic spasm). Epilepsy type was classified as focal in seven patients, combined focal and generalized in two, generalized in four, and unknown in one. An
Table 1. Comparison of clinical characteristics between patients with and without epilepsy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with epilepsy (n=14)</th>
<th>Patients without epilepsy (n=89)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>11/14 (78.6)</td>
<td>40/97 (41.2)</td>
<td>0.023</td>
</tr>
<tr>
<td>Age at diagnosis (yr)</td>
<td>5.4 (0.42–11.0)</td>
<td>4.4 (0.05–20.5)</td>
<td>0.913</td>
</tr>
<tr>
<td>Follow-up duration (mo)</td>
<td>76.8 (12.4–211.3)</td>
<td>73.0 (0.5–282.4)</td>
<td>0.397</td>
</tr>
<tr>
<td>Family history of NF1</td>
<td>7/14 (50)</td>
<td>34/89 (38.2)</td>
<td>0.558</td>
</tr>
<tr>
<td>Family history of epilepsy</td>
<td>5/14 (35.7)</td>
<td>1/89 (1.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Learning disability</td>
<td>9/14 (64.3)</td>
<td>22/89 (24.7)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

MRI findings

- Optic glioma                     | 0/14 (0)                      | 5/89 (5.6)                      | 1.000   |
- Other brain tumors               | 0/14 (0)                      | 4/89 (4.5)                      | 1.000   |
- Vascular abnormalities           | 1/14 (7.1)                    | 4/89 (4.5)                      | 0.526   |
- UBO                              | 7/14 (50)                     | 53/89 (59.6)                    | 0.567   |
- Other abnormalities*             | 2/14 (14.3)                   | 3/89 (3.4)                      | 0.135   |
- Abnormalities except UBO         | 3/14 (21.4)                   | 15/89 (16.9)                    | 0.698   |
- Abnormalities including UBO      | 8/14 (57.1)                   | 56/89 (62.9)                    | 0.779   |

Values are presented as number (%) or median (range).

NF1, neurofibromatosis type 1; MRI, magnetic resonance imaging; UBO, unidentified bright object.

*Subdural hemorrhage and Chiari malformation type 1 were observed in the epileptic group and cerebral atrophy, chronic infarction, and increased volume of both hippocampi were observed in the non-epileptic group.

### Table 2. Epilepsy characteristics in patients with neurofibromatosis type 1

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Sex</th>
<th>Family history of seizure</th>
<th>Age at seizure onset (yr)</th>
<th>Seizure characteristic</th>
<th>MRI at seizure onset</th>
<th>EEG at seizure onset</th>
<th>No. of AED</th>
<th>DRE</th>
<th>LD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>+</td>
<td>2</td>
<td>Focal</td>
<td>0–1/year</td>
<td>+</td>
<td>+</td>
<td>Moyamoya syndrome</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>–</td>
<td>4.4</td>
<td>Focal</td>
<td>1/year</td>
<td>–</td>
<td>+</td>
<td>Diffuse slowing</td>
<td>Focal</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>–</td>
<td>5.8</td>
<td>Focal</td>
<td>2/week</td>
<td>–</td>
<td>+</td>
<td>Focal</td>
<td>Focal</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>+</td>
<td>5</td>
<td>Focal</td>
<td>1/year</td>
<td>–</td>
<td>SECTS</td>
<td>–</td>
<td>Focal</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>–</td>
<td>3.8</td>
<td>Focal</td>
<td>1/month</td>
<td>–</td>
<td>–</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>–</td>
<td>10.9</td>
<td>Focal</td>
<td>3/month</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>Focal</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>–</td>
<td>5.8</td>
<td>Focal</td>
<td>3/month</td>
<td>–</td>
<td>SECTS</td>
<td>Type 1 CM</td>
<td>Focal</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>–</td>
<td>18.9</td>
<td>Generalized</td>
<td>3/month</td>
<td>–</td>
<td>–</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>–</td>
<td>6.4</td>
<td>Generalized</td>
<td>10–20/day</td>
<td>–</td>
<td>CAE</td>
<td>3 Hz spike and wave</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>–</td>
<td>1.3</td>
<td>Generalized</td>
<td>3/day</td>
<td>–</td>
<td>–</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>+</td>
<td>5.9</td>
<td>Generalized</td>
<td>1/year</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Normal</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>–</td>
<td>11.1</td>
<td>Focal/generalized</td>
<td>1/year</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>Normal</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>+</td>
<td>7.3</td>
<td>Focal/generic</td>
<td>2–4/day</td>
<td>+</td>
<td>LGS</td>
<td>+</td>
<td>Focal/generic</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>+</td>
<td>1.1</td>
<td>Unknown</td>
<td>2–4/day</td>
<td>–</td>
<td>IS+LGS</td>
<td>–</td>
<td>Focal/generic</td>
</tr>
</tbody>
</table>

MRI, magnetic resonance imaging; EEG, electroencephalography; AED, anti-epileptic drug; DRE, drug-refractory epilepsy; LD, learning disability; SE, status epilepticus; ES, epilepsy syndrome; UBO, unidentified bright object; SECTS, self-limited epilepsy with centrotemporal spike; CM, Chiari malformation; CAE, childhood absence epilepsy; LGS, Lennox-Gastaut syndrome; IS, infantile spasm.

Epilepsy syndrome was present in five patients: Lennox-Gastaut syndrome (n = 2), self-limited epilepsy with centrotemporal spikes (n = 2), and childhood absence epilepsy (n = 1).

EEG findings at the time of seizure onset were normal in six patients (42.9%), while four (28.6%) had focal epileptiform discharges, two (14.3%) had generalized, and two (14.3%) had generalized and focal. Epileptogenic zones presumed from seizure semiology and interictal EEG findings were not concordant with the location of structural abnormalities or UBOs in brain MRI of all nine patients with focal seizures (Supplementary Table 1). Among
the six patients who had follow-up MRI, findings remained normal in three patients with UBOs and one with normal findings at the time of seizure onset, although two of them still had seizures.

One patient was lost to follow-up. Among the 13 patients with follow-up data, nine (69.2%) were seizure-free for at least the last 12 months. Ten patients (71.4%) received treatment with an average of 1.9 AEDs. DRE was observed in two patients (14%): one had focal impaired awareness motor seizure or focal to bilateral seizures with seizure frequency of 1 to 3 per month and the other had Lennox-Gastaut syndrome with atypical absence, atonic, and focal to bilateral seizures despite treatment with five AEDs. Both had intellectual disability and UBOs in MRI. The UBO locations were not concordant with the location of epileptiform discharges in EEG. Five patients (35.7%) had status epilepticus and one of them died due to it.

3. Epilepsy risk factors in NF1

Epilepsy risk factors in NF1 were analyzed (Table 3). Age at diagnosis, sex, family history of NF1, family history of epilepsy, learning disability, and brain MRI findings including UBO and other structural abnormalities were included as variables in the multiple logistic regression analysis. The ORs of learning disability (OR, 4.54; 95% CI, 1.17 to 17.54; \(P = 0.028\)) and family history of epilepsy (OR, 39.65; 95% CI, 3.78 to 416.53; \(P = 0.002\)) were significantly higher in patients with epilepsy. Structural brain abnormalities were not found to be significant risk factors.

Discussion

In this study, we analyzed clinical characteristics and epilepsy risk factors in patients with NF1 at a single tertiary center. The prevalence of epilepsy in NF1 patients was 13.6%, higher than the general population (0.45% to 1%) [18,19]. Our findings are consistent with previous reports regarding prevalence rates ranging between 4.1% and 14.1% [6-8,10,20,21]. Serdaroglu et al. [10] reported the prevalence of epilepsy as 4.1% among pediatric patients with NF1 from a single center in Turkey, whereas a nationwide survey in Japanese NF1 children reported 13.8% [21]. The incidence of epilepsy varied due to different cohorts and inclusion criteria used. In this study, we used data from a single tertiary care center with a rare disease and pediatric epilepsy clinics, which might have resulted in our relatively higher prevalence of epilepsy. To minimize selection bias, nationwide data under a universal criterion for the epilepsy group is needed.

Although the mechanism of seizures in NF1 has not been clarified, NF1-related intracranial pathology such as brain tumors, moyamoya syndrome, and hydrocephalus may partially explain the higher prevalence of seizures in patients with NF1 [5-7]. In addition, temporal lobe epilepsy, often associated with focal cortical dysplasia, hippocampal sclerosis, and dysembryoplastic neuroepithelial tumor, has been reported in some patients with NF1 and most have shown considerable improvement or seizure freedom after surgical resection of the epileptogenic lesion [8,22,23].

However, in this study, the proportion of structural abnormalities did not differ between the patients with and without epilepsy. Among the 14 patients with epilepsy, only three had structural abnormalities other than UBOs and their localization was not concordant with epileptogenic foci. Nine patients with focal seizures showed discordance between the location of the presumed epileptogenic zone according to seizure semiology and interictal EEG and MRI findings (Supplementary Table 1). The incidence of UBOs was not significantly different with patients with and without epilepsy (50% vs. 59.6%). Moreover, we found no relation between the localization of UBOs and epileptiform discharges on EEG in seven patients with UBOs. Furthermore, in some patients, epilepsy type \((n = 6, 42.9\%)\) and EEG findings \((n = 8, 57.1\%)\) were generalized. Our results are consistent with a recent study that found that the most common MRI findings in NF1 epilepsy patients are UBOs (80%), followed by normal (20%), and that the localization of UBOs and EEG abnormalities was discordant [10]. Likewise, Santoro et al. [6] reported the presence and location of UBOs were not related to seizures among the 17 patients with epi-

**Table 3. Epilepsy risk factors in neurofibromatosis type 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>1.05</td>
<td>0.87–1.26</td>
<td>0.643</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.26</td>
<td>0.04–1.58</td>
<td>0.144</td>
</tr>
<tr>
<td>Family history of NF1</td>
<td>1.13</td>
<td>0.23–5.62</td>
<td>0.884</td>
</tr>
<tr>
<td>Family history of epilepsy</td>
<td>39.65</td>
<td>3.78–416.53</td>
<td>0.002</td>
</tr>
<tr>
<td>Learning disability</td>
<td>4.54</td>
<td>1.17–17.54</td>
<td>0.028</td>
</tr>
<tr>
<td>UBOs</td>
<td>3.18</td>
<td>0.65–15.50</td>
<td>0.152</td>
</tr>
<tr>
<td>Other MRI findings except UBOs</td>
<td>0.74</td>
<td>0.09–5.95</td>
<td>0.777</td>
</tr>
</tbody>
</table>

CI, confidence interval; NF1, neurofibromatosis type 1; UBO, unidentified bright object; MRI, magnetic resonance imaging.
epilepsy and NF1, suggesting that UBOs do not play any role in seizure pathogenesis. In a recent animal study of seizure susceptibility in NF1, a higher proportion of $Nf1^{+/−}$ mice had behavioral seizures after kainic acid or pilocarpine challenge, with shorter seizure latency and longer seizure duration, even though hippocampal damage was similar in both $Nf1^{+/−}$ and wild type controls [11]. These results suggest that in addition to structural changes, other mechanisms, such as genetic mutation, may also contribute to epileptogenesis in patients with NF1.

Several hypotheses support genetic susceptibility as a contributing seizure mechanism in NF1. Neurofibromin deficiency leads to increased Ras activity, the mechanistic target of rapamycin activation, and GABA-ergic signaling in the inhibitory circuit, which might contribute to neuronal hyperexcitability [10,24]. Neurofibromin also plays a role in cortical development, including synaptogenesis and synaptic plasticity; therefore, the lack of it may be related to abnormal cortical development and seizure development [3,25]. NF1 knockout models demonstrate abnormal cortical lamination, increased neuronal heterotopia, and microdysgenesis of the hippocampus [25], which could explain the increased occurrence of structural abnormalities such as dysembryoplastic neuroepithelial tumors and cortical malformation in some NF1 patients with epilepsy. Furthermore, the role of ion channel dysfunction leading to hyperexcitability has been suggested in NF1 mouse model [26,27]. Further study using the $Nf1^{+/−}$ mouse model will assist in determining epileptogenicity in NF1 [28].

Although the patients in our study showed heterogeneous seizure characteristics, they tended to have focal seizures (n = 9, 64.3%) and relatively good outcomes. Nine (64.3%) patients remained seizure-free for > 1 year. These findings are similar to previous studies that reported good seizure control with just one AED or without AED therapy in 60% of patients with NF1 [20,21]. Likewise, Santoro et al. [6] reported that eight of 16 patients receiving AED therapy were seizure-free for > 1 year and none had DRE. In contrast, Ostendorf et al. [7] reported that patients with epilepsy required an average of 2.4 and 3.4 medications to manage their generalized and focal seizures, respectively, and only 34% of patients were well-controlled with one or no AEDs. In our study, DRE was observed in two patients (14.3%) and both had intellectual disability and UBOs on MRI. In a study by Vivarelli et al. [29], four of 14 (29%) patients with epilepsy presented with DRE, and all four patients had severe mental retardation and three of these had malformations of cortical development. Another study including 14 patients with NF1 and DRE showed MRI abnormalities in all patients but one [30]. These heterogeneous results may be attributed to different patient characteristics including the presence of intellectual disability and structural brain abnormalities such as cortical dysplasia and NF1-related brain tumors among the study groups, as these abnormalities can cause medically refractory seizures.

In our study, epilepsy syndrome was present in five patients: self-limited epilepsy with centrotemporal spikes, childhood absence epilepsy, infantile spasm, and Lennox-Gastaut syndrome. In addition to these, juvenile myoclonic epilepsy and Doose syndrome have been reported from the NF1 patients in previous reports [6-8]. However, no correlation between NF1 and epilepsy syndrome was found.

To determine more specific evidence of epileptogenesis in NF1, we analyzed the epilepsy risk factors and found a strong association of both learning disability and family history of seizures with epilepsy in NF1 patients. This supports a previous study that reported an increased risk of learning disability in children with NF1 and seizures [6,10]. A higher frequency of learning difficulty in the seizure group, regardless of epilepsy severity, suggests that learning disability in NF1 might co-occur with epilepsy as a genetic predisposition rather than as a causal relationship [10]. Cognitive deficits appear to be related to synaptic dysfunction because of signaling dysfunction of Ras—the extracellular signal-regulated kinase (ERK), cyclic adenosine monophosphate, and dopamine homeostasis rather than a macroscopic structural lesion [3,26]. Increased GABA-ergic signaling caused by dysfunction of Ras–ERK signaling accounts for learning deficits in an NF1 mouse model [12]. Furthermore, increased GABA-ergic signaling in local inhibitory circuits could cause seizure development by altering inhibitory/excitatory balance [26]. A higher frequency of epilepsy in family history of patients with epilepsy also supports the role of genetic susceptibility in epileptogenesis. However, only two patients in our study had a family member diagnosed with NF1 and epilepsy; therefore, other genetic predispositions to epilepsy may be related to seizure threshold in addition to the effect of the NF1 gene. As NF1 genetic testing in all study patients could not be performed, the association between the type and location of NF1 variants and seizures could not be analyzed. Further studies to compare genotypes between NF1 patients with and without epilepsy may clarify the genotype-phenotype correlation.

In conclusion, epilepsy is more common in patients with NF1 compared to the general population. Although the clinical characteristics of epilepsy in NF1 are heterogeneous, most patients had focal seizures and good seizure outcome. No significant difference in structural brain abnormalities between patients with and without epilepsy was found. In addition, epilepsy in NF1 is associated with a family history of epilepsy and learning disability, which contribute to a genetic mechanism that might be associated with cellular or synaptic changes in the brain and epileptogenesis in NF1 pa-
tients. Further studies are needed to clarify the intrinsic role of NF1 in epileptogenesis in NF1 patients.

**Supplementary materials**

Supplementary materials related to this article can be found online at https://doi.org/10.26815/acn.2020.00283.

**Conflicts of interest**

Soonhak Kwon is an editor-in-chief of the journal, but he was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Conceptualization: AS and YJL. Data curation: JCB. Formal analysis: AS. Funding acquisition: YJL. Methodology: SKH. Project administration: AS. Visualization: YJL. Writing-original draft: AS. Writing-review & editing: JCB, SKH, SK, and YJL.

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**References**


Purpose: The present study aimed to elucidate the clinical characteristics of children with tuberous sclerosis complex (TSC) in Korea using the Tuberous Sclerosis-Associated Neuropsychiatric Disorders (TAND) checklist to evaluate the comorbidities of neurocognitive and socioemotional problems in the Korean clinical setting.

Methods: A survey based on the TAND checklist was administered to 58 children with TSC receiving treatment on an outpatient basis. Their medical records and test results were retrospectively examined.

Results: At the time of TAND administration, 35 (64.8%) of the participants had focal epilepsy, three (5.6%) had generalized epilepsy, six (11.1%) had infantile spasms, and seven (13.0%) had Lennox–Gastaut syndrome. The most frequently reported behavioral problem was difficulty getting on with other people of similar age (38/58, 65.5%). Twenty patients had received previous diagnoses of psychiatric disorders, six of whom had received two or more concurrent diagnoses. A further evaluation after testing with the TAND checklist identified new psychiatric disorders in two patients. Among the 35 children who underwent a formal evaluation of intelligence, 27 (77.1%) exhibited intellectual disability. Of the school-aged patients, 65.6% (21/32) experienced difficulties with mathematics and 56.3% (18/32) with spelling. Difficulty dual-/multi-tasking (27/58, 46.6%) and low self-esteem (18, 31.0%) were the most frequent neuropsychological and psychosocial issues, respectively.

Conclusion: Our findings indicate that patients with TSC tend to experience neurocognitive and socioemotional difficulties, and regular screening for TAND using the TAND checklist can be helpful for managing children with TSC in the clinical setting.

Keywords: Tuberous sclerosis; Epilepsy; Pediatrics; Mental disorders
Introduction

Tuberous sclerosis complex (TSC)—a representative hereditary neurocutaneous syndrome—is a genetic disorder affecting numerous organs including the brain, eyes, heart, kidneys, lungs, and skin. The hallmark of TSC is the involvement of the central nervous system (CNS) with a wide clinical spectrum varying from severe intellectual disability and intractable epilepsy to normal intelligence and lack of seizures. CNS involvement in patients with TSC is mainly associated with epilepsy, intellectual disability, and autism spectrum disorder (ASD) [1-3]. Furthermore, many of the multidimensional problems experienced by patients with TSC change over time, substantially affecting quality of life. Thus, an overall understanding of physical, cognitive, and mental health is necessary to ensure continuous and systematic management of symptoms in this population [3,4]. To further this aim, the neurocognitive panel of the 2012 International TSC Consensus Conference recommended that individuals with TSC should be screened for comorbid conditions once per year [5]. In 2015, De Vries et al. [6] proposed the Tuberous Sclerosis-Associated Neuropsychiatric Disorders (TAND) checklist.

In the present study, we aimed to investigate trends of neurocognitive and socioemotional disorders in Korean children with TSC using a Korean version of the TAND.

Materials and Methods

1. Patients

The present study included children and adolescents ( < 19 years of age) who were diagnosed with TSC based on established clinical criteria and who underwent outpatient treatment at the Severance Children’s Hospital Department of Pediatric Neurology or the National Health Insurance Service Ilsan Hospital Department of Pediatrics Developmental Delay Clinic between March 2008 and February 2018. The TAND was described to the parents of all participants, and 58 children whose parents provided consent were included.

2. Methods

The TAND checklist (United States English version) was translated into Korean in cooperation with the original authors [6]. A survey was constructed based on the translation, and medical staff with appropriate knowledge and experience completed the survey after consent was provided for study participation. The TAND checklist is composed of diverse items related to behavioral, psychiatric, cognitive, learning, neuropsychological, and psychosocial issues that may occur in patients with TSC. Specifically, the version of the TAND checklist used in the present study contained 19 items relevant to behavioral issues (Supplementary material).

The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Yonsei University Severance Hospital and National Health Insurance Service Ilsan Hospital (IRB No. 4-2018-0111 and NHIMC 2016-04-011).

Results

1. Patient characteristics

Of the 58 participants, 26 (44.8%) were boys and 32 (55.2%) were girls, with a boy-to-girl ratio of 0.81:1. The median age at TAND checklist administration was 9.2 years (interquartile range, 4.1 to 14.6). Fifty-four patients (93.1%) had been diagnosed with epilepsy and were receiving treatment at pediatric neurology departments. Fourteen patients (24.1%) had a history of infantile spasms (IS). Most patients were diagnosed with TSC based on clinical criteria, although diagnoses were confirmed via TSC1 or TSC2 genetic testing in 18 patients (31.0%; four with TSC1 gene mutations and 14 with TSC2 gene mutations).

2. Clinical features of epilepsy in pediatric patients with TSC

Of the 58 participants, 54 (93.1%) had a history of epilepsy treatment, including 25 boys (46.3%) and 29 girls (53.7%; boy-to-girl ratio, 0.86:1). The median age at first seizure was 0.7 years (interquartile range, 0.3 to 2.0) (Table 1).

At TAND checklist administration, three patients (5.6%) were seizure-free and required no further treatment for epilepsy, whereas 35 patients (64.8%) were undergoing relevant treatment for focal epilepsy, and three patients (5.6%) were for generalized epilepsy.

Six children (11.1%) had IS and seven (13.0%) had Lennox–Gastaut syndrome (LGS) at the time of the study (Table 1).

When the TAND checklist was administered, one-fifth of the patients (n = 17, 21.5%) were experiencing intractable seizures at least once daily. The mean number of drugs used at the time of the study was 2.1 ± 1.32 (range, 0 to 6). Thirteen patients (24.1%) had attempted to follow a ketogenic diet (KD), and 15 (27.8%) had undergone epilepsy surgery. Three patients had both attempted to follow a KD and had undergone epilepsy surgery (Table 1).

3. TAND checklist results

1) Behavioral level

Of the 19 behavior-related items, challenges interacting with peers...
was the most frequently reported (38/58, 65.5%), followed by language delay or impairment (36/58, 62.1%). More than half of all patients experienced inattentiveness (31/58, 53.4%) and mood swings (29/58, 50.0%) (Fig. 1A). Twenty-four patients (24/58, 41.3%) have had further evaluation or support for related problems and 14 parents of participants (14/58, 24.1%) wished further evaluation for their children.

2) Psychiatric level
Twenty patients had previously been diagnosed with a specific psychiatric disorder based on diagnostic criteria and six patients had more than two disorders (Fig. 1B). There were seven patients (12.1%) with attention deficit hyperactivity disorder (ADHD), six (10.3%) with ASD, four (6.8%) with anxiety disorder including panic, phobia, separation anxiety disorder, while three had depressive disorder. Two patients had been diagnosed with obsessive compulsive disorder (OCD) and one patient had schizophrenia (SPR). Two children had been diagnosed with ADHD, depressive disorder, and anxiety disorder and had begun treatment for their respective conditions based on further evaluations after administration of the TAND checklist.

3) Intellectual level
Formal evaluation and confirmation of intelligence was possible in 35 patients (60.3%). Of these patients, five (14.3%) exhibited normal intelligence (intelligence quotient [IQ] > 80), two (5.7%) had borderline intellectual ability (IQ, 70 to 80), and the rest (80.0%) had intellectual disability in various degrees (Fig. 2).

Fifty-three of the 58 parents of participants responded to questions regarding concern for their child’s intellectual ability, with 45 guardians (84.9%) expressing concerns. Additionally, 34 guardians (58.6%) intended to seek further evaluation or support regarding the child’s cognitive function. These results indicate that the TAND checklist motivated approximately 60% of guardians to seek additional evaluation or support for previously unidentified issues relevant to intellectual disability.

4) Academic level
Thirty-two participants were of school age (> 6 years of age). Twenty-one participants (65.6%) experienced challenges with mathematics, 18 (56.3%) had difficulties with spelling, and 15 (28.2%) each with reading and writing (Fig. 1B). None of the five patients with normal intelligence reported learning difficulties. Twenty participants were reported to have been considered for additional support in school such as further help or an individual educational plan.

5) Neuropsychological level
The most commonly impaired function was multi-tasking (27/58, 46.6%), followed by executive functioning skills (26/58, 44.8%), and attention/visuospatial task performance (23/58 for each ability, 39.7%) (Fig. 1A). One of the five patients with normal intelligence experienced challenges with multi-tasking, whereas the remaining patients with normal intelligence did not report neuropsychological difficulties.

6) Psychosocial level
Low self-esteem was reported by 18 patients (31.0%), very high levels of stress between parents leading to significant relationship difficulties were reported by 13 patients (22.4%), and very high levels of stress in families were reported by 12 patients (20.7%) (Fig. 1B). Even four patients with normal intelligence who had no neuropsychological difficulties in other levels reported low self-esteem or stress in families.
Difficulties getting on with other people of similar age
Absent or delayed onset of language to communicate
Difficulty paying attention or concentrating
Mood swings
Very rigid or inflexible or not liking change on routines
Repeating words or phrases
Anxiety
Impulsivity
Repetitive behaviors
Restlessness or fidgetiness
Difficulties with eating
Overactivity/hyperactivity
Poor eye contact
Sleep difficulties
Temper tantrums
Extreme shyness
Depressed mood
Self-injury

Further evaluation plan
Evaluation history

Fig. 1. Detailed results of the Tuberous Sclerosis-Associated Neuropsychiatric Disorders checklist in 58 pediatric participants with tuberous sclerosis complex. (A) Number of participants per item for the behavioral and neuropsychological levels. (B) Number of participants per item for the psychiatric, academic, and psychological levels. ASD, autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; IEP, individual educational plan.

https://doi.org/10.26815/acn.2020.00220
Discussion

Curatolo et al. [2] described TAND as an umbrella term encompassing diverse impairments at the behavioral, psychiatric, cognitive, learning, neuropsychological, and psychosocial levels. In the present study, we tried to focus on diverse aspects of TSC patients not only on epilepsy but also on other neuropsychiatric problems using the Korean version of TAND checklist. We directly communicated with the original authors of TAND-related articles [6,7] and translated with back-translation process over 10 months and at last administered it to 58 Korean children with TSC. We observed considerable challenges in behavioral, psychiatric, cognitive, learning, neuropsychological, and psychosocial functioning in TSC patients using it.

TSC is known to be associated with developmental delays, as well as cognitive, learning, and behavioral disorders that are independent of epilepsy [1,2,8,9]. But these TAND characteristics are not frequently evaluated, treated, or managed in a systematic fashion, resulting in a gap between the clinical needs of patients and available treatment options. To reduce the treatment gap, neuropsychiatric assessment should be performed at each lifespan stage in clinical setting in treating TSC patients [6,10].

Diverse behavioral problems can be seen on TSC patients and shared experience of these characteristics can be helpful to dealing with these patients for the parents and clinicians. In psychiatric level, ASD occurs in 40% to 50% of patients, and 30% to 50% of patients are diagnosed with ADHD. Previous studies have also reported that psychiatric disorders such as anxiety/panic disorder, depression, OCD, and SPR are often comorbid with TSC [2]. Comparing with that, in the present study, ASD, ADHD, and anxiety occurred in 10.3% (6/58), 12.1% (7/58), and 6.8% (4/58) of patients, respectively. These values are much lower than those reported by previous studies, although we suspect underreporting due to limited awareness of psychiatric disorders in the patient population. Future studies should aim to enhance awareness of comorbid psychiatric disorders in pediatric patients with TSC using screening tests such as the TAND checklist; subsequent intensive evaluation and intervention should then occur as necessary.

In intellectual level, 28 (80.0%) of the 35 patients whose IQ was assessed with a formal intelligence test had intellectual disability in the present study. Intellectual disabilities are reported that majorly correlate with intractable epilepsy in TSC patients; 60.7% of these patients had intractable epilepsy with previous treatments including using ≥ 3 drugs, KD, or surgery. Cognitive impairment in TSC patients is revealed to be more severe in patients whose seizures begin at an earlier age, those with drug-resistant epilepsy, those who experience various seizure types, and those with more brain tubers [11-13]. Cognitive impairment also tends to be more severe as the number of drugs increased. A similar trend was also observed in patients who had attempted to follow a KD or had undergone surgery for drug-resistant epilepsy, and in patients diagnosed with IS or LGS [14,15]. One of the seven patients with normal or borderline intelligence had no history of epilepsy, whereas the rest were confirmed to have focal epilepsy that was well-controlled with drug therapy.

Learning disability belongs to the different aspect of TSC. In academic issue, learning disability occurs in 30% of school-aged patients with TSC. Even if intelligence is normal, patients often experience challenges with reading, writing, arithmetic, and spelling, which necessitates individualized learning plans [2,6]. Although none of the seven patients with normal intelligence reported learning-related problems, many patients with cognitive impairment did experience learning challenges. More than half of school-aged patients with TSC experienced challenges with mathematics or spelling (65.6% and 56.3%, respectively), and as many as 28.2% of patients reported difficulties with reading and writing. These findings are consistent with previously published results [3,6,8].

Some studies have previously revealed the following frequently documented neuropsychological issues in patients with TSC:

![Fig. 2. Intellectual level of 32 school-age participants with tuberous sclerosis complex.](https://doi.org/10.26815/acn.2020.00220)
memory impairment, challenges with maintaining or shifting attention, challenges with multi-tasking, and impairments in visuo-spatial working memory, executive function, and orientation [2,6]. We also observed that patients experienced challenges with multi-tasking (27/58, 46.6%), as well as impairments in executive function (26/58, 44.8%), attentiveness (23/58, 39.7%), and visuo-spatial task performance (23/58, 39.7%). An examination of cases in which formal neuropsychological tests were performed following evaluation with the TAND checklist revealed a discrepancy between neuropsychological conditions reported by guardians on the TAND checklist and the results of formal tests.

The limitations of this study include its small sample size and one-time point assessment. Larger longitudinal observations and correlations between the TAND checklist and formal neuropsychological evaluations could support more reliable and useful information for the assessment and treatment of individuals of TSC. Accordingly, future studies should investigate the correlation between the results of the TAND checklist and formal neuropsychological tests to identify the source of this discrepancy.

In this study, we performed the first translation and administration of the TAND checklist Korean version. The screening results will aid clinicians in referring patients for further evaluation and in subsequent treatment planning. The translation of the checklist in Korean will also aid in across country comparisons. Future studies should investigate the validity of the TAND checklist by examining correlations between TAND responses and the results of formal neuropsychological tests.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.26815/acn.2020.00220.

Conflicts of interest

Hoon-Chul Kang is an associate editor, Joon Soo Lee and Heung Dong Kim are editorial board members of the journal, but They was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Author contribution

Conceptualization: HDK and HJC. Data curation: SP and SE. Formal analysis: SP and JSL. Funding acquisition: HJC. Methodology: HCK, HDK, and HJC. Project administration: HJC. Visualization: SP and SE. Writing-original draft: SP. Writing-review & editing: HJC.

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References

Risk Factors for Chronic Kidney Disease in Pediatric Patients with Epilepsy

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Purpose: The aim of the treatment of epileptic seizures is to achieve a seizure-free state without adverse effects. The mainstays of seizure treatment are anticonvulsant medication, diet therapy, and surgery. Antiepileptic drugs and a ketogenic diet are associated with various types of medical adverse effects, including chronic kidney disease (CKD). We aimed to identify the characteristics of pediatric epilepsy patients who developed CKD and to determine the possible mechanisms.

Methods: We included 816 patients who underwent medical treatment for epilepsy and were followed-up for at least 3 years at a tertiary hospital. The patients were divided into CKD and non-CKD groups. The data were assessed using a multivariate Cox proportional hazards model to identify the factors associated with CKD among patients undergoing epilepsy treatment.

Results: Initial high serum creatinine levels (hazard ratio [HR], 13.927; P=0.010), microscopic hematuria on initial urinalysis (HR, 10.047; P=0.001), developmental delay (HR, 11.929; P=0.000), and interictal epileptiform discharges on initial electroencephalography (generalized interictal epileptiform discharges: HR, 38.395, P=0.003; focal interictal epileptiform discharges: HR, 19.252, P=0.006) were associated with increased CKD risk.

Conclusion: CKD was more likely to develop in patients who presented with initial kidney dysfunction and developmental delay, and was related to epilepsy itself. The abovementioned factors may increase CKD risk through decreased brain function, which may lead to decreased activity and, hence, to relatively poor hygiene and voiding function. Moreover, patients with pre-existing kidney disease were more vulnerable to CKD development.

Keywords: Epilepsy; Renal insufficiency, chronic; Anticonvulsants; Risk; Child

Introduction

Epilepsy is a brain disorder which implies an enduring predisposition to unprovoked seizures [1,2]. The main focus of epilepsy treatment is satisfactory seizure control with minimal adverse effects [3]. Epilepsy treatments in children and adolescents are usually prescribed for at least 2 years (and for life-time in some cases), for which adverse effect control is of utmost importance [2,4].

Patients undergoing long-term treatment with antiepileptic drugs (AEDs) may develop other diseases, as well as adverse effects from the drugs, which may limit AED usage [4,5]. Several AEDs undergo hepatic metabolism and are excreted via urine. Lamotrigine, phenobarbital, and lacosamide, which are often used in clinical practice, are examples of this pharmacokinetics. On the other hand, levetiracetam and topiramate remain unchanged before being excreted via urine. Long-term use of these drugs can
cause side effects on the kidneys. Some common adverse effects include nephrotoxicity, calciuria, and other events related to the kidneys [3,5]. However, and despite the abovementioned, only a few patients with long-term AED treatment develop chronic kidney disease (CKD).

In this paper, we investigated the characteristics of epilepsy patients who developed CKD. Through this study, we aimed to identify risk factors for CKD and analyze which factors should be considered in the treatment plan of patients with these characteristics.

Materials and Methods

1. Patients
A total of 816 patients who underwent medical treatment for epilepsy, including anticonvulsant medication, diet therapy, or surgery, and who were followed up for > 3 years from 2016 to 2019 at the Korea University Guro Hospital were included in this study.

2. Group definition
The patients were divided into two groups: CKD and non-CKD. CKD was defined as decreased kidney function shown by glomerular filtration rate (GFR) of < 60 mL/min/1.73 m², or the presence of markers of kidney damage, or both, of at least 3 months of duration regardless of underlying cause [6]. The markers of kidney damage considered for CKD diagnosis were urinary sediment abnormality, abnormal histological findings, and structural abnormalities detected by imaging [6,7]. The process of group classification is briefly explained in a flow diagram (Fig. 1).

3. Pharmacological therapy
Pharmacological treatment was usually initiated after epilepsy diagnosis and report of recurrent unprovoked seizures. The AED dose was gradually increased until the lowest effective maintenance dose to minimize adverse effects. If seizures persisted despite an AED up-titration to the maximum tolerated dose, the AED was switched to an alternative AED monotherapy. If two or three sequential monotherapies failed, polytherapy was offered. Polytherapy was considered earlier when prognostic factors indicated difficulty of treatment by monotherapy, considering the severity of the epilepsy. The cumulative treatment time of the administered AED was investigated to analyze its association with CKD.

4. Ketogenic diet
Despite the lack of a well-defined mechanism of action, several reports suggest that a ketogenic diet reduces seizure frequency [8,9]. In our center, the ketogenic diet was used as a treatment for drug-resistant pediatric epilepsy. In particular, a ketogenic diet was prescribed in cases of intractable epilepsy with myoclonic seizures, atonic seizures, or mixed seizures, as is the case in Lennox-Gastaut syndrome (LGS). In these patients, the classical ketogenic diet, which is based on a 3:1 ratio and a 4:1 ratio of high fat to low carbohydrate and to protein, respectively, was used [8,9].

5. Statistical analysis
Continuous data are presented as mean ± standard deviation and were evaluated using an independent samples t-test. Categorical data are presented as percentages and were evaluated using the chi-square test (Table 1). The Cox proportional hazards model was used to compare the variables between CKD and non-CKD groups (Table 2). Data in Table 2 were investigated using univariate analysis. Finally, all data in Table 2 were analyzed using the adjusted multivariate Cox proportional hazards model for variables such as age, sex, follow-up duration, number of AEDs, ketogenic diet, each AED’s treatment time, initial laboratory findings, electroencephalography (EEG) findings, initial magnetic resonance imaging (MRI) findings, and developmental delay. The risk difference was reported as odds ratios with 95% confidence interval (CI). All reported P values are two-sided. All statistical analyses were performed using SPSS version 20 (IBM Co., Armonk, NY, USA). Results were considered statistically significant if P < 0.05.

6. Ethical approval
The study procedures were approved and monitored by the Institutional Review Board of the Korea University Medical Center (IRB No. 2020GR0312) and were conducted in compliance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

![Fig. 1](https://doi.org/10.26815/acn.2020.00213)
Table 1. Baseline characteristics of the patients classified by CKD status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n = 816)</th>
<th>Non-CKD (n = 796)</th>
<th>CKD (n = 20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mo)</td>
<td>14.97 ± 6.55</td>
<td>14.95 ± 6.56</td>
<td>15.95 ± 6.27</td>
<td>0.383a</td>
</tr>
<tr>
<td>Male sex</td>
<td>487 (59.68)</td>
<td>473 (59.42)</td>
<td>14 (70.00)</td>
<td>0.341</td>
</tr>
<tr>
<td>Follow-up duration (mo)</td>
<td>117.92 ± 46.72</td>
<td>117.93 ± 46.74</td>
<td>117.58 ± 46.82</td>
<td>0.898b</td>
</tr>
<tr>
<td>AED medications</td>
<td>2.17 ± 1.27</td>
<td>2.15 ± 1.27</td>
<td>2.65 ± 1.31</td>
<td>0.055c</td>
</tr>
<tr>
<td>Ketogenic diet</td>
<td>11 (1.35)</td>
<td>10 (1.26)</td>
<td>1 (5.00)</td>
<td>0.240d</td>
</tr>
<tr>
<td>AED medication period (mo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>48.13 ± 62.98</td>
<td>47.80 ± 62.65</td>
<td>61.40 ± 75.34</td>
<td>0.569e</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>33.33 ± 43.12</td>
<td>33.04 ± 43.00</td>
<td>45.05 ± 47.23</td>
<td>0.087f</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>30.35 ± 47.28</td>
<td>30.49 ± 47.57</td>
<td>24.80 ± 34.40</td>
<td>0.909g</td>
</tr>
<tr>
<td>Topiramate</td>
<td>17.54 ± 38.48</td>
<td>17.49 ± 38.52</td>
<td>20.40 ± 37.84</td>
<td>0.675h</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>6.56 ± 24.21</td>
<td>6.34 ± 23.84</td>
<td>15.25 ± 35.86</td>
<td>0.051i</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>0.83 ± 7.85</td>
<td>0.84 ± 7.94</td>
<td>0.50 ± 2.01</td>
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<tr>
<td>Lamotrigine</td>
<td>20.63 ± 46.50</td>
<td>20.61 ± 46.48</td>
<td>21.40 ± 48.36</td>
<td>0.939k</td>
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<tr>
<td>Clobazam (BDZ)</td>
<td>11.18 ± 35.29</td>
<td>10.79 ± 34.60</td>
<td>26.75 ± 55.49</td>
<td>0.101l</td>
</tr>
<tr>
<td>Perampanel</td>
<td>1.51 ± 6.41</td>
<td>1.48 ± 6.35</td>
<td>3.00 ± 8.57</td>
<td>0.016m</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>4.38 ± 18.56</td>
<td>4.38 ± 18.65</td>
<td>4.20 ± 15.09</td>
<td>0.957n</td>
</tr>
<tr>
<td>Initial laboratory findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>11.71 ± 3.66</td>
<td>11.70 ± 3.61</td>
<td>12.08 ± 5.38</td>
<td>0.579o</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.47 ± 0.19</td>
<td>0.47 ± 0.19</td>
<td>0.55 ± 0.33</td>
<td>0.324p</td>
</tr>
<tr>
<td>Microscopic hematuria</td>
<td>31 (3.80)</td>
<td>27 (3.39)</td>
<td>4 (20.00)</td>
<td>0.005q</td>
</tr>
<tr>
<td>Dipstick proteinuria</td>
<td>217 (26.59)</td>
<td>211 (26.51)</td>
<td>6 (30.00)</td>
<td>0.727r</td>
</tr>
<tr>
<td>Inter-ictal epileptiform discharges on initial EEG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No inter-ictal epileptiform discharges</td>
<td>367 (44.98)</td>
<td>365 (45.85)</td>
<td>2 (10.00)</td>
<td>0.006</td>
</tr>
<tr>
<td>Generalized inter-ictal epileptiform discharges</td>
<td>64 (7.84)</td>
<td>61 (7.66)</td>
<td>3 (15.00)</td>
<td>0.001s</td>
</tr>
<tr>
<td>Focal inter-ictal epileptiform discharges</td>
<td>385 (47.18)</td>
<td>370 (46.48)</td>
<td>15 (75.00)</td>
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<tr>
<td>Abnormal background activity on initial EEG</td>
<td>120 (14.71)</td>
<td>111 (13.94)</td>
<td>9 (45.00)</td>
<td>0.001t</td>
</tr>
<tr>
<td>Brain abnormality on initial MRI</td>
<td>159 (19.49)</td>
<td>151 (18.97)</td>
<td>8 (40.00)</td>
<td>0.039u</td>
</tr>
<tr>
<td>Kidney abnormality on initial US</td>
<td>31 (3.80)</td>
<td>26 (3.27)</td>
<td>5 (25.00)</td>
<td>0.001v</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>100 (12.25)</td>
<td>88 (11.06)</td>
<td>12 (60.00)</td>
<td>0.000w</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%).
CKD, chronic kidney disease; AED, antiepileptic drug; BUN, blood urea nitrogen; EEG, electroencephalography; MRI, magnetic resonance imaging; US, ultrasonography.

*Mann-Whitney U test; †Fisher exact test.

Write informed consent by the patients was waived due to a retrospective nature of our study.

Results

1. Patients’ clinical characteristics at baseline

Table 1 presents the descriptive baseline characteristics of the study sample. The mean age was 14.97 ± 6.55 years and females comprised 59.68% of the included patient population. The follow-up period was 117.92 ± 46.72 months from the initial visit to our center. These patients were treated with 2.17 ± 1.27 AEDs during the follow-up period. All patients received AED treatment, and 11 (1.35%) were prescribed ketogenic diet in addition. The details of each AED’s treatment time is described in Table 1. Regarding laboratory findings, all patients underwent blood tests and urinalysis periodically during AED treatment to detect adverse effects. The blood urea nitrogen and the creatinine levels were within the normal range at the initial evaluation (blood urea nitrogen 11.71 ± 3.66; creatinine 0.47 ± 0.19). Thirty-one patients (3.80%) had microscopic hematuria and 217 (26.59%) had dipstick proteinuria at baseline. In the initial EEG test, 64 (7.84%) and 385 patients (47.18%) showed generalized and focal epileptiform discharges, respectively. Moreover, background activity was abnormal in 120 (14.71%) patients. All patients in this study underwent brain MRI at diagnosis, and 159 (19.49%) presented structural anomalies of the brain, including hippocampal sclerosis, ventriculomegaly, periventricular leukomalacia, and masses. Developmental delay was reported in 100 patients (12.25%) at initial evaluation, and 31
(3.80%) presented abnormal findings on abdominal kidney ultrasonography.

There were significant differences in microscopic hematuria, interictal epileptiform discharges, abnormal background activity on initial EEG, brain abnormalities on initial MRI, kidney abnormalities on initial ultrasonography, developmental delay at baseline, and Perampanel treatment time between CKD and non-CKD groups. The treatment time of Perampanel was significantly different between the two groups in an independent samples t-test. Perampanel undergoes oxidation mediated by hepatic metabolism and is excreted via feces (48%) and urine (22%). It is well known that patients treated with perampanel are prone to urinary tract infection and hyponatremia [10,11]. In contrast, treatment time of other AEDs did not show statistical significance.

2. Factors influencing CKD incidence among patients’ initial characteristics and epilepsy therapy

To assess the factors influencing kidney function, the multivariate Cox proportional hazards model was performed. All the parameters in Table 2 were candidate variables for this analysis. The univariate Cox proportional hazards model results shown in Table 2 indicated statistical significance for microscopic hematuria, interictal epileptiform discharges, abnormal background activity on initial EEG, brain abnormalities on initial MRI, kidney abnormality on initial ultrasonography, and developmental delay at baseline between the CKD and non-CKD groups. However, the multivariate Cox proportional hazards model using backward stepwise (likelihood ratio) selected four prognostic factors associated with an increased risk of CKD: serum creatinine (hazard ratio [HR], 13.927; 95% CI, 1.857 to 104.455; \( P = 0.010 \)); microscopic hematuria on

| Variable | Univariate | | Multivariate |
|---|---|---|
| **Variable** | HR (95% CI) | P value | HR (95% CI) | P value |
| Age (mo) | 0.928 (0.855–1.007) | 0.073 |  | |
| Female:Male | 0.639 (0.246–1.665) | 0.360 |  | |
| AED medications | 1.133 (0.837–1.532) | 0.419 |  | |
| Ketogenic diet | 6.705 (0.874–51.466) | 0.067 |  | |
| AED medication period (mo) |  |  |  | |
| Valproic acid | 0.997 (0.991–1.003) | 0.341 |  | |
| Levetiracetam | 1.002 (0.994–1.011) | 0.562 |  | |
| Oxcarbazepine | 0.996 (0.986–1.005) | 0.358 |  | |
| Topiramate | 0.999 (0.989–1.009) | 0.802 |  | |
| Phenytoin | 0.999 (0.989–1.009) | 0.802 |  | |
| Lamotrigine | 0.995 (0.986–1.004) | 0.282 |  | |
| Clobazam [BDZ] | 1.003 (0.995–1.011) | 0.507 |  | |
| Perampanel | 1.015 (0.966–1.066) | 0.549 |  | |
| Vigabatrin | 0.990 (0.965–1.016) | 0.458 |  | |
| Initial laboratory findings |  |  |  | |
| BUN (mg/dL) | 1.038 (0.924–1.165) | 0.533 |  | |
| Creatinine (serum, mg/dL) | 1.458 (0.162–13.148) | 0.737 | 13.927 (1.857–104.455) | 0.010 |
| Microscopic hematuria | 6.595 (2.188–19.877) | 0.001 | 10.047 (2.642–38.202) | 0.001 |
| Dipstick proteinuria | 1.068 (0.409–2.787) | 0.893 |  | |
| Inter-ictal epileptiform discharges on initial EEG |  |  |  | |
| No inter-ictal epileptiform discharges |  |  |  | |
| Generalized inter-ictal epileptiform discharges | 8.684 (1.448–52.059) | 0.018 | 38.395 (3.394–434.346) | 0.003 |
| Focal inter-ictal epileptiform discharges | 6.932 (1.584–30.341) | 0.010 | 19.252 (2.331–158.964) | 0.006 |
| Abnormal background activity on initial EEG | 3.781 (1.563–9.147) | 0.003 |  | |
| Brain abnormality on initial MRI | 2.706 (1.104–6.631) | 0.030 |  | |
| Kidney abnormality on initial US | 7.219 (2.614–19.393) | 0.000 |  | |
| Developmental delay | 12.347 (5.045–30.217) | 0.000 | 11.929 (3.476–40.939) | 0.000 |

HR, hazard ratio; CI, confidence interval; AED, antiepileptic drug; BUN, blood urea nitrogen; EEG, electroencephalography; MRI, magnetic resonance imaging; US, ultrasonography.
initial urinalysis (HR, 10.047; 95% CI, 2.642 to 38.202; \( P = 0.001 \)); developmental delay (HR, 11.929; 95% CI, 3.476 to 40.939; \( P = 0.000 \)); and interictal epileptiform discharges on initial EEG (generalized interictal epileptiform discharges [HR, 38.395, 95% CI, 3.394 to 434.346; \( P = 0.003 \]), focal interictal epileptiform discharges [HR, 19.252; 95% CI, 2.331 to 158.964; \( P = 0.006 \)].

In Kaplan-Meier curves, which are widely used to estimate the survival function, the probability of CKD differed significantly according to the number of risk factors. The survival curve decreased rapidly as the number of significant risk factors increased (Fig. 2).

**Discussion**

In this study aimed at determining risk factors for CKD in pediatric epilepsy patients, we detected four significant risk factors, namely, initial creatinine, microscopic hematuria, interictal epileptiform discharges, developmental delay.

All patients with ongoing AED treatment underwent urinalysis to detect adverse effects such as nephrotoxicity, hypercalciuria, and nephrolithiasis. A statistical analysis was performed to confirm whether initial hematuria affects kidney function and the multivariate Cox proportional hazards model showed that microscopic hematuria was significantly different between the CKD group (four patients [20.00%]) and the non-CKD group (27 patients [3.39 %]). Microscopic hematuria is a common clinical manifestation in children, adolescents, and young adults, with its incidence ranging from 0.18% to 16.1% according to previous studies [12-14]. Hematuria can either be an isolated finding unaccompanied by other urinary abnormalities or be accompanied by urinary abnormalities such as proteinuria, hypertension, and elevated serum creatinine level [13,14]. Persistent isolated microscopic hematuria can have either a glomerular or a non-glomerular origin, including several kidney disease entities [12,13]. In fact, among the 20 patients in the CKD group, four patients presented glomerulonephritis in the histopathologic examination. The four cases of glomerulonephritis were classified as Henoch-Schönlein nephritis (grade III), focal segmental endocapillary proliferative glomerulonephritis, focal segmental glomerulosclerosis, and minor glomerular change on renal histological examination. Additionally, four patients reported recurring urinary tract infections and nephrolithiasis. The causes of hematuria mentioned above increase the risk of CKD [14]. In other studies, 0.7% of patients with persistent isolated microscopic hematuria developed end-stage kidney disease compared with 0.04% in the control group, yielding an adjusted HR of 18.5 (95% CI, 12.4 to 27.6) [14].

The multivariate Cox proportional hazard model result showed that increased serum creatinine levels significantly increased the risk of CKD (HR, 13.927; 95% CI, 1.857 to 104.455; \( P = 0.010 \)). Because creatinine is excreted from the circulation mainly by renal filtration, it is strongly correlated with GFR [15-17]. An increase in serum creatinine reflects an impaired renal ability to remove waste products from the body [16]. The creatinine concentration in decreases progressively with decreased GFR, and its diagnostic performance has been shown to be good, even for the detection of minor deteriorations of the renal function [15,16]. Hence, creatinine is a strong predictor of CKD progression [16].

In this study on the prediction of risk factors of CKD, the EEG results were analyzed by classifying them into different findings.
rather than into a clinical diagnosis. Regarding the presence of interictal epileptiform discharges, the HR of generalized interictal epileptiform discharges was 38.395, and that of focal interictal epileptiform discharges was 19.252 in the CKD group compared to the non-CKD group for initial interictal EEG findings. Patients with interictal epileptiform discharges on EEG tend to have clinical seizure events in contrast to those without. Recurrent clinical seizure events impair cognitive abilities and neurological development. Regarding background activity, when there was a disorganization, the HR was 4.201, indicating borderline significance. Abnormal background activity on the EEG includes a lack of the expected organization corresponding to age, multifocal spikes, and loss of normal physiological hallmarks, like sleep spindles [18-20]. These EEG findings are seen in most cases where the brain is structurally and functionally deteriorated, including in LGS, Rett syndrome, and West syndrome. In this study, seven patients with CKD who experienced intractable epilepsy (e.g., LGS, Rett syndrome, West syndrome, Devic syndrome, Wolf-Hirschhorn syndrome) were bedridden [18-20]. The comparison was not statistically significant; however, it is possible that abnormal background activity acts as a significant risk factor in larger patient groups considering its borderline significance. In general, only 29% to 55% of epilepsy patients have epileptiform abnormalities on a single routine outpatient EEG. Therefore, even if normal EEG findings are reported in the first examination, abnormal findings often appear in the second and third examinations. However, in the present study we only analyzed the initial EEG results to assess the risk of CKD at the initial planning of diagnosis and treatment.

In addition, 12 (60%) patients in CKD group, including those with intractable epilepsy, had developmental delays. In such cases, the patients’ brain dysfunction may not directly unable to have normal daily lives, it may lead to poor sanitation and urinary retention without voluntary urination [21]. These patients might be more vulnerable to nephrotoxicity induced by the long-term administration of AEDs. The patients’ decreased voiding function may lead to residual urine. Among these patients, some developed urinary tract stones and recurrent urinary tract infections, which leads to acute kidney injury and affects renal function, and which can contribute to the development of CKD. In the present case, the statistically significant HR related to developmental delay was 11.929.

In conclusion, the risk of CKD increases in cases of epilepsy with high creatinine and microscopic hematuria associated with kidney damage, and with restricted daily activity due to a decreased brain function. In this study on factors associated with an increased risk of CKD, the abovementioned factors had statistically significant results while AED-related factors did not. In the long-term treatment of epilepsy patients, it is important to perform regular kidney function evaluations and to practice regular urine voiding to prevent the development of CKD, in addition to following-up potential AED adverse effects.

This study has some limitations. The study was retrospective in nature, and the sample was not randomized. Moreover, the patients were prescribed different AEDs not based on the medical condition alone, but also for social reasons. In addition, it is possible that factors including AED history, ketogenic diet, and abdominal ultrasonography were not statistically significant owing to the relatively small number of patients in the CKD group. As shown in the study results, AEDs that lead to nephrotoxicity might act as risk factors for patients with vulnerability factors for CKD. Further study is need to validate the risk of CKD generated by AEDs, ketogenic diet, EEG findings, brain function, and kidney factors in larger CKD patient groups.

Conflicts of interest

Baik-Lin Eun is an editorial board member of the journal, but he was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Author contribution

Conceptualization: JP, CHY, and BLE. Data curation: BLE. Formal analysis: JP, JHB, and BLE. Methodology: JP. Writing-original draft: JP. Writing-review & editing: JP, JHB, CHY, and BLE.

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References

Recurrence of Epilepsy and Related Risk Factors after the Discontinuation of Antiepileptic Drugs in Children: A 10-Year Single-Center Study

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Purpose: The criteria for discontinuing antiepileptic drugs (AEDs) in children with well-controlled epilepsy remain unclear. This study sought to identify the recurrence rate of epilepsy after the discontinuation of AEDs and the risk factors associated with recurrence.

Methods: We retrospectively reviewed the records of 441 children who discontinued AEDs at our department of pediatrics from August 2007 to July 2017. AED tapering was performed in patients who were seizure-free for more than 2 years after taking AEDs, and patients were monitored for 1 year after the discontinuation of AEDs.

Results: We found that 87 patients (87/441, 19.7%) experienced seizure recurrence within 1 year after the discontinuation of AEDs. Among them, 38 patients (38/87, 43.7%) experienced recurrence during AED tapering. The recurrence of seizures was related to the patient’s age at AED onset and when seizures were controlled, a history of seizure recurrence after previous discontinuation of AEDs or a seizure episode during AED administration, and no improvement of electroencephalographic (EEG) findings.

Conclusion: The recurrence rate within 1 year after the discontinuation of AEDs was almost 20%, and nearly half of the recurrences took place during the tapering period. We recommend caution when considering whether to discontinue AEDs in patients with a history of seizure recurrence after AED discontinuation, a seizure episode during AED administration, or no (or slight) improvement of EEG findings.

Keywords: Epilepsy; Recurrence; Child; Risk factors; Anticonvulsants

Introduction

Epilepsy is a disease whose diagnosis and treatment are continuously undergoing development. Currently, epileptic symptoms can be controlled in 70% to 80% of affected patients with the administration of various antiepileptic drugs (AEDs) [1]. The rate of symptom recurrence is being increasingly diminished by the advancement of AEDs and drugs that can measure serum concentration [2]. However, AEDs are associated with poor drug compliance due to their numerous adverse effects and the need to consume them daily. These drawbacks are of particular concern for school-age children, in whom AEDs cause drowsiness, fatigue, and attention deficits that may impair their language and cognitive development [3].
Prior research has investigated whether the timing of discontinuing AED administration to pediatric patients can be calibrated so as to diminish the probability of seizure recurrence and, hence, the need to resume AED therapy [4]. For instance, Strozzi et al. [5] reported a seizure-free period of to 2 years to be suggestible for AED discontinuation. However, as only a few studies have considered the discontinuation of AEDs and the risk factors associated with seizure recurrence in children, the timing of AED discontinuation in pediatric patients remains controversial.

In this study, we sought to identify the recurrence rates of epilepsy after discontinuation of AEDs in pediatric patients. We also identified the risk factors associated with the recurrence of epilepsy.

**Materials and Methods**

1. **Patients**
The present retrospective analysis was conducting using data obtained from the patients’ medical records. Among the patients that were admitted to the Department of Pediatrics at the Jeonbuk National University Hospital of South Korea and diagnosed with epilepsy between August 31st 2007 and July 31st 2017, patients (except for neonatal children under 1 month) who showed two or more unprovoked attacks or who visited the hospital with 1st attack and showed clear abnormal findings related to clinical symptoms on electroencephalography (EEG) were selected as participants for this study. They administrated of AEDs for at least 2 years and monitored for 1 year after tapering of AEDs. EEGs obtained at the time of diagnosis and before the discontinuation of AEDs were analyzed and neuroimaging was tested in patients except 56 patients who failed sedation treatment, rejected examinations, or were presumed to be epilepsy syndrome in EEG findings.

Since the timing of tapering AEDs depends on the type of epilepsy, we considered a seizure-free period as at least 2 years for types with good prognosis such as benign rolandic epilepsy, and more than 2 years for types with incurable prognosis such as infantile spasms or Lennox-Gastaut syndrome. However, we attempted to taper AEDs if there was a clear improvement in EEG or when the caregiver requested an end to treatment for their children whose epilepsy had been well-controlled for at least 2 years in types with incurable prognosis. AED tapering was carried out with a gradual and even drug dose reduction over a mean period of more than 8 weeks and if more than two medications were administered, one by one was reduced. All patients were monitored for 1 year after the discontinuation of AEDs.

The definition of recurrence of epilepsy was defined when there was unprovoked seizure within 1 year after the discontinuation of AEDs. However, it was determined that recurrence occurred when the typical 3 Hz spike-and-wave complex was shown on the follow-up EEG regardless of clinical symptoms in the case of absence seizure.

A total of 630 patients were initially selected for participation in this study. We subsequently excluded 42 patients with limited data due to them having been transferred from a different hospital after the initiation of AED treatment, 27 patients who were less than a month old upon admission, 82 patients who received less than 1 year of follow-up, and 38 patients who diagnosed with juvenile myoclonic epilepsy, which is known to recur soon after the discontinuation of AEDs. Data obtained from the final 441 patients were analyzed to identify the recurrence rates of epilepsy after discontinuation of AEDs and the risk factors associated with the recurrence.

This study was performed with approval from the Institutional Review Board of Jeonbuk National University Hospital Research Council (CUH2020-01-037). Written informed consent by the patients was waived due to a retrospective nature of our study.

2. **Risk factors**
We considered the association between epilepsy recurrence and the following factors associated with the recurrence: sex, age-related factors (the age at seizure onset, at which the AED administration began, at maintaining a longer interval than the existing seizure period [which seizures were controlled], and at discontinuation of AEDs), episodes of seizure during AED administration, number of AEDs administered, family history of epilepsy, history of febrile convulsion and status epilepticus, history of epilepsy recurrence after previous discontinuation of AEDs, pretreatment seizures frequency, radiographic abnormalities, EEG analysis, and neurological disability.

3. **Statistical analysis**
The SPSS version 25 (IBM Co., Armonk, NY, USA) was used to perform all statistical analyses. The risk factors for the recurrence of epilepsy were analyzed using the chi-square test, independentsamplest test, and Kaplan-Meier survival analysis with the log-rank test. Data are presented as the mean ± standard deviation and P values < 0.05 were considered to indicate statistical significance.

**Results**

1. **Overall results**
After the discontinuation of AEDs, 87 (19.7%) of 441 patients experienced recurrences within 1 year. Among 87 patients with recurrence within 1 year, 53 men and 34 women and 38 patients (43.7%) experienced recurrences during tapering period, 22 pa-
tients (25.3%) relapsed within 6 months after discontinuation of AEDs and 27 patients (31.0%) relapsed within 6 months to 1 year. The average time of recurrence after AED discontinuation was 0.7 ± 1.0 year. Of these, 24.1% had recurrence after previous discontinuation of AEDs, 67.8% had episodes of seizure during AED administration, 65.5% used a single type of AED to control seizure, and 16.1% showed radiographic abnormalities. Also 92.0% showed abnormal findings in EEGs at the time of diagnosis and 38.7% showed no change or an aggravation of the abnormalities.

2. Risk-factor analysis (univariate analysis)
We analyses risk factors by clinical characteristics (Table 1).

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Recurrence no. /total no. (%)</th>
<th>Pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td>0.542</td>
</tr>
<tr>
<td>Male</td>
<td>53/238 (22.2)</td>
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<tr>
<td>Female</td>
<td>34/203 (16.7)</td>
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<td>Age at</td>
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<td>Seizure onset</td>
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<td>Infancy</td>
<td>15/51 (29.4)</td>
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<td>Early childhood</td>
<td>26/149 (17.4)</td>
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<tr>
<td>Late childhood</td>
<td>28/171 (16.3)</td>
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<tr>
<td>Adolescence</td>
<td>22/70 (31.4)</td>
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<td>Infancy</td>
<td>7/27 (25.9)</td>
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<tr>
<td>Early childhood</td>
<td>25/130 (19.2)</td>
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<tr>
<td>Late childhood</td>
<td>28/195 (14.3)</td>
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<tr>
<td>Early childhood</td>
<td>11/49 (22.4)</td>
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<tr>
<td>Late childhood</td>
<td>21/117 (17.9)</td>
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<tr>
<td>Adolescence</td>
<td>55/275 (20.0)</td>
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<tr>
<td>Recurrence after previous discontinuation of AEDs</td>
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<td>No</td>
<td>66/398 (16.7)</td>
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</tr>
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<td>21/43 (48.8)</td>
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<tr>
<td>Seizure episode while taking AEDs</td>
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<tr>
<td>No</td>
<td>28/233 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>59/208 (28.3)</td>
<td></td>
</tr>
</tbody>
</table>

AED, antiepileptic drug; EEG, electroencephalogram.

1) Sex
The recurrence rates according to sex were 22.2% for boys and 16.7% for girls. Sex was not significantly associated with recurrence (P = 0.542).

2) Age-associated factors
The associations between the seizure recurrence and the age at seizure onset, age at which AEDs were first administered, age at which the seizures were controlled and age at AED discontinuation were analyzed. The mean ages at seizure onset, first administration of AEDs, control of seizures and AED discontinuation were 6.3 ± 4.0, 7.3 ± 3.9, 8.4 ± 4.1, and 11.9 ± 4.4 years of age, respectively. For these analyses, the patients were divided into subgroups according to age: infancy (1 month to 1 year of age), early childhood (1 to 5
years of age), late childhood (6 to 10 years of age), and adolescence (11 to 21 years of age).

The recurrence rates according to the age at first seizure were 29.4% for infancy, 17.4% for early childhood, 16.3% for late childhood, and 31.4% for adolescence. The differences in recurrence according to the age at first seizure were not significant ($P = 0.174$).

The recurrence rates according to age at which AEDs were first administered were 25.9% for infancy, 19.2% for early childhood, 14.3% for late childhood, and 30.3% for adolescence. The recurrence rates were significantly higher when AEDs were first administered in infancy or adolescence than in early or late childhood ($P = 0.012$).

The recurrence rates according to the age when seizure was controlled were 23.0% for infancy, 18.6% for early childhood, 13.6% for late childhood, and 20.0% for adolescence. The recurrence rates were significantly higher when seizures were controlled in infancy or adolescence than in early or late childhood ($P = 0.008$).

While the recurrence rates according to the age at AED discontinuation were not available for patients in infancy, they were 22.4% for early childhood, 17.9% for late childhood, and 20.0% for adolescence. The age at AED discontinuation did not significantly affect rates of recurrence ($P = 0.870$).

3) Family history of epilepsy
We identified 32 patients with family histories of epilepsy; the recurrence rate among these patients was 15.6%. The recurrence rate was 20.0% among patients without a family history of epilepsy. The difference between these rates was nonsignificant ($P = 0.421$).

4) Histories of febrile convulsion and status epilepticus
The recurrence rate was 17.3% among patients with histories of febrile convulsion and 20.8% among those with no history of febrile convulsion. There was no statistically significant difference between these recurrence rates ($P = 0.165$). Among the 30 patients with histories of status epilepticus, the recurrence rate was 26.7%; while this rate was slightly higher than that among patients without histories of status epilepticus (19.2%), the difference was nonsignificant ($P = 0.245$).

5) Recurrence after previous discontinuation of AEDs
Among the 43 patients with histories of recurrence after previous discontinuation of AEDs, the recurrence rate was 48.8%. This rate was significantly higher than that among patients without histories of recurrence after previous discontinuation of AEDs (16.7%, $P < 0.001$) (Fig. 1).

6) Pretreatment seizure frequency
Seizure frequency didn’t be obtained from 50 patients. Except them, the recurrence rates of epilepsy were 19.1% among the patients with one seizure before treatment, 21.0% among those with two to nine seizures, and 12.5% among those with 10 or more seizures. The differences between these rates were nonsignificant ($P = 0.620$).

7) AEDs
The mean duration of AED administration was 4.5 ± 2.3 years and when compared by dividing the duration of taking anticonvulsants by 3 years, the recurrence rate for those less than 3 years was 31.7% and for those over 3 years was 20.21%, which was nonsignificant ($P = 0.763$). A single type of AED was used to control seizure for 324 patients—the majority; two types of AEDs were used in 87 cases, three types in 25 cases, and four or more types in five cases; the recurrence rates were 17.6%, 22.9%, 36.0%, and 20.0%, respectively. No statistically significant differences in these recurrence rates were found ($P = 0.395$).

8) Episodes of seizure during AED administration
The recurrence rate was significantly lower among patients with no seizures during AED administration (12.0%) than among those who had episodes of seizure during AED administration (28.3%, $P < 0.001$) (Fig. 2).

9) Radiographic abnormalities
Neuroimaging was tested in patients except 56 patients who failed sedation treatment, rejected examinations, or were presumed to be epilepsy syndrome in EEG findings. Of the 385 patients who re-
ceived brain computed tomography and magnetic resonance imaging (MRI) examinations, abnormalities associated with epilepsy were found in 65 (Table 2), while none were found in 320. Their recurrence rates were 21.5% and 22.8%, respectively. The difference between these rates was not statistically significant ($P = 0.805$).

10) EEG analysis
EEGs obtained at the time of diagnosis were analyzed abnormalities were found in 409 patients, while none were found in 32; their recurrence rate was 19.6% and 21.9%, respectively. While the recurrence rate was higher among patients with normal EEG findings, the difference between the two rates was not statistically significant ($P = 0.805$). Among the patients with EEG abnormalities, background EEG aberrations were found in 77 patients, focal epileptiform discharges were found in 261 and generalized epileptiform discharges were found in 71.

All patients underwent EEG examinations more than once before the discontinuation of AEDs, and the changes were compared with the initial finding. Among the 409 patients with abnormal EEGs at the time of diagnosis, 337 showed improvements, while 72 showed either no change or an aggravation of the abnormalities; their recurrence rates were 14.5% and 43.1%, respectively. The rate of recurrence was significantly higher among the patients whose EEG showed no change or an aggravation ($P = 0.039$) (Fig. 3).

11) Neurological disability
To assess neurological disability presented by the patients, we analyzed data obtained from neurological examination, language tests, and developmental tests. Neurological abnormalities ranging from developmental delay to mental retardation or cerebral palsy were identified in 112 patients. The recurrence rate among these patients was 25.9% and that among the patients without neurological disability was 17.6%. Though a trend was observed, the difference between these rates was nonsignificant ($P = 0.065$).

12) Classification of epilepsy syndrome
Patients that could be classified as special epileptic syndrome were classified by EEG examination, and there were 48 benign rolandic seizures, 28 absent seizures, three Lennox-Gastaut syndrome, and six photosensitive epilepsy. The recurrence rate was 16.7% (8/48) in benign rolandic seizures, 21.4% (6/28) in absent seizures, 66.7% (2/3) in Lennox-Gastaut syndrome and 33.3% (2/6) in photosensitive epilepsy, but the difference between these rates was not statistically significant ($P = 0.085$).
Discussion

The present study observed the overall recurrence rate within 1 year after the discontinuation of AEDs to be 19.7% (87/441). When evaluated according to the timing of AED discontinuation, the highest rate of recurrence was observed during AED tapering 43.7% (38/87). We further identified the following factors as being significantly associated with recurrence of epilepsy: the age at which AEDs were first administered and seizures were controlled, a history of epilepsy recurrence after previous discontinuations of AEDs, an episode of seizure during AED administration, and no improvement in EEG findings across AED administration.

When timing the discontinuation of AEDs, medical factors as well as other individual factors should be considered [6]. The will of patients and their caregiver, their economic conditions, the adverse effects of drugs, and comorbidity can also affect the decision to discontinue AED administration. Numerous studies have sought to elucidate the factors associated with the recurrence of epilepsy after the discontinuation of AEDs to help inform this decision. For instance, upon reviewing the results from various studies, the American Academy of Neurology reported in 1996 that seizure-free period of 2 to 5 years, normal results from neurological examination, and the normalization of EEG during treatment lessened the risk of recurrence [7]. In addition, the risk of recurrence reportedly increases when the cause of epilepsy is symptomatic [8-10] and decreases when patients show an early response to the first administration of AED [8,11].

Regarding the differences in the risk of recurrence according to the age at seizure onset, several reports have found that the risk increases in adolescence; Shinnar et al. [12] defined this period as beginning at the age of 12, while Dooley et al. [13] and Chung et al. [14] considered adolescence to begin at the age of 10. Emerson et al. [15] reported that the recurrence rate is higher when the patient experiences his or her first seizure at the age of 2 years or younger. Although recurrence rates according to the age at seizure onset were higher in the infancy and adolescence relative to those in early and late childhood, the differences were not statistically significant in this study.

In some studies, there was no association between recurrence and histories of recurrence after previous discontinuations of AEDs and when epilepsy recurred after previous discontinuations of AED, the re-administration of AEDs lead to the remission of epilepsy [13,16]. However, in our study, the rate of recurrence was 48.8% among the patients with histories of epilepsy recurrence after previous discontinuations of AED, while a rate of 16.7% was observed among the patients without epilepsy recurrence after previous discontinuations of AED.

As for episodes of seizure during administering AEDs, Chung et al. [14] reported the recurrence of seizures during administering AEDs did not appear to be related to relapse. However, Specchio and Beghi [11] reported a connection as in this study.

This study performed an analysis of EEG results obtained at the time of diagnosis and before the discontinuation of AEDs. While Shinnar et al. [12] and Emerson et al. [15] reported that EEG abnormalities identified before discontinuations of AED treatment cannot predict the risk of recurrence, we found that there was a significantly higher recurrence rate among patients whose EEG results did not improve than among those whose results did (43.1%, 14.5%, respectively). Hence, our study observed that improvement in EEG findings (across treatment) is more predictive of recurrence than is the EEG obtained at the time of diagnosis.

Hippocampal atrophy or sclerosis identified with MRI is reportedly associated with a high rate of epileptic recurrence [2]. On the other hand, Lossius et al. [17] reported that abnormal findings from MRI are not predictive factors for epilepsy recurrence. Similarly, our study found the recurrence rate to be 21.5% in the presence of radiographic abnormalities and 22.8% in their absence, but it was not a significant predictor of epileptic recurrence. That’s because the abnormal MRI was considered as a case of simple ventriculomegaly as well as lesions with a high recurrence rate such as hippocampal sclerosis.

According to some studies [6,11,18], neurological disability increases the risk of epilepsy recurrence. While the present study found that the recurrence rate of epilepsy was higher among patients with neurological disability than among those without them (25.9%, 17.6%, respectively), this difference was nonsignificant.

As for the number of AEDs administered to control seizures, some studies [14,15] have reported an increase in the recurrence rate if multiple anticonvulsants were administered, but in other study [12], the risk of recurrence did not increase even if multiple AEDs were administered like our study.

There are some limitations in our study. It is limited by its retrospective nature as well as by its use of data obtained from a single institute. It was further limited by only having monitored the patients’ treatment when the patients revisited our hospital through the outpatient clinic or emergency room. Prospective studies that perform more regular monitoring of the patients’ clinical progress and an accurate analysis of treatment compliance are warranted. As the follow-up period for pediatric patients tends to be limited—unlike that for adult patients—and such patients generally visit a different department when they become adults, collaboration with the Department of Neurology will be needed in the future to analyze the long-term recurrence rates of epilepsy. Moreover, differences in the diagnosis rate caused by the development of EEG and
radiographic equipment during the 10 years of follow-up period, as well as differences in the treatment rate caused by changes in therapeutic agents, could have biased our study results. Finally, there are a few epilepsy syndromes that have a high probability of recurrence so that AEDs discontinuation is not suggested. These include Lennox-Gastaut syndrome, Dravet syndrome or severe brain lesions such as brain cell migration disorder [19]. However, we attempted to taper AEDs in our study if there was a clear improvement in EEG or when the caregiver requested an end to treatment for their children whose epilepsy had been well-controlled for at least 2 years without the improvement of EEG.

However, compared to some studies that have analyzed the factors affecting the recurrence of epilepsy in Korea [2,20], our study included a relatively large number of pediatric patients and that is the strength of this study.

In conclusion, the risk of recurrence may be high if (1) the patient was an infant or an adolescent when AEDs were first administered or when the seizures were controlled; (2) no (or less) improvement in EEG finding during AED administration; (3) he/she experienced seizure during AED administration; or (4) he/she has a history of epilepsy recurrence after previous discontinuation of AEDs. Therefore, the discontinuation of AEDs should be considered with greater care for these patients especially during tapering period.

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**Conflicts of interest**

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

**Author contribution**

Conceptualization: SJK. Data curation: JHC and SJK. Formal analysis: JHC. Methodology: SJK. Project administration: SJK. Visualization: JHC. Writing-original draft: JHC. Writing-review & editing: SJK.

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Trends in Pediatric Meningitis in South Korea during 2009 to 2017: Analysis of the Health Insurance Review and Assessment Service Database

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Purpose: Previous estimates of the cause- and age-specific frequency of pediatric meningitis in Korea were mainly derived from single- and multi-center studies. Herein, we used data on the number of cases of bacterial and viral meningitis from the Health Insurance Review and Assessment Service database to examine time- and sex-related trends.

Methods: We extracted data on meningitis diagnoses registered in the Health Insurance Review and Assessment Service from 2009 to 2017, using Korean Standard Classification of Disease and Cause of Death codes. Information on 202,254 children aged 0 to 18 years was extracted. Detailed demographic and disease information was available for 84,543 children who underwent hospitalization.

Results: Among all hospitalized patients, 2166, 36,155, and 46,192 children were diagnosed with bacterial, viral, or other types of meningitis, respectively. There were 30 cases of fungal meningitis and another 30 cases of meningitis attributable to other pathogens. The number of cases of bacterial and viral meningitis was highest among infants (1,087 [50.2%]) and patients in their early childhood (12,949 [35.9%]), respectively. Meningitis outbreaks were most likely to occur during the summer, and boys were more susceptible to meningitis than girls. The following pathogens most commonly caused infant meningitis: group B Streptococcus, Escherichia coli, and type B Haemophilus influenzae.

Conclusion: This study reports the number of pediatric meningitis cases, stratified by age, disease type, and month/year. The present findings contribute to a better understanding of pediatric meningitis in Korea and provide a foundation for future research to identify the risk factors for this disease.

Keywords: Child; Meningitis; Republic of Korea; Disease outbreaks

Introduction

Meningitis is a condition in which the meninges surrounding the brain and spinal cord are inflamed [1,2]. Among other infectious diseases that occur in children, meningitis is the most common cause of central nervous system disease [1]. Meningitis is associat-
ed with a high risk of systemic infection, which can lead to serious sequelae; thus, careful diagnosis and treatment are paramount [3-5]. It is broadly categorized as bacterial meningitis, viral meningitis, and meningitis due to other cause (e.g., parasites or fungi), and it tends to occur as a result of spread of infection to the meninges from elsewhere in the body [1,6].

Bacterial meningitis requires rapid diagnosis and treatment as it is associated with a high risk of sepsis, which has a mortality rate of 10% [2,7,8]. Viral meningitis is more common than bacterial meningitis and it tends to present as a relatively less severe disease, although it can lead to serious complications and long-term disability [9-12]. Fungal and parasitic meningitis are rare but can progress to severe disease via the mediation of immune suppressors [1,13].

Previous reports on the cause- and age-stratified frequency of pediatric meningitis in Korea have primarily originated from single- and multi-center studies [14,15]. In contrast, the present study used data on the frequency of bacterial and viral meningitis obtained from the Health Insurance Review and Assessment Service (HIRA) database to examine time- and sex-related trends. Recently, various studies have been started in relation to the HIRA database, but there has been no recent prevalence study in children in Korea. Since this study included data across all ages and medical institutions, it can provide an objective and accurate prediction of the prevalence and future trends of current diseases.

Materials and Methods

1. Data sources
The HIRA database is a data repository, built using information communication technology [16], that captures information of claimants under Korea’s National Health Insurance scheme, including details of disease screening, diagnostic evaluation and medical resources required, and socio-economic status. Annually, data from 87,000 medical claims become available for research purposes. Use of these data for this study was approved by the Institutional Review Board of Chung-Ang University Hospital. The study was designed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Chung-Ang University (IRB No.: 1921-002-360). Written informed consent by the patients was waived due to a retrospective nature of our study.

In this study, disease classification was performed according to the Korean Standard Classification of Disease and Cause of Death (KCD-7), which was revised in 2015, based on the World Health Organization’s International Classification of Disease and Cause of Death [17]. We extracted the medical and demographic data of patients with meningitis who were registered with the HIRA from 2009 to 2017; this disease included 43 distinct entities. Diagnoses of meningitis were classified as bacterial, viral, fungal and parasitic, and other types; diagnoses with 0 patient were excluded (Table 1).

2. Study population
Domestic pediatric patients aged 0 to 18 years were included and classified based on their diagnoses (Table 1). In total, the data on 19,277 cases of bacterial, 155,959 cases of viral, 245 cases of fungal and parasitic, and 158,056 cases of other types of meningitis were extracted. Duplicate records were removed.

In general, meningitis is diagnosed and treated in an in-patient setting; thus, this study only included records from certified tertiary hospitals, general hospitals, and other types of hospitals. In addition to the above reasons, in this paper, since the HIRA database was used through the KCD-7 code, we tried to exclude patients who had diagnosed names only by clinical diagnosis. At this stage, the study sample comprised 2,166 cases of bacterial, 36,155 cases of viral, 30 cases of fungal and parasitic, and 46,192 cases of others type of meningitis (Fig. 1).

The same method was applied to extract and categorize each diagnosis into subgroups. The HIRA data only classified patients by their respective age, and not according to different age groups. However, in our analyses, we followed the staging system of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, which classifies children based on age ranges [18].

3. Statistical analysis
Data were extracted from the HIRA database and examined using SAS Enterprise version 9.2 (SAS Institute, Cary, NC, USA). All statistical analyses were performed using SPSS version 20 for Windows (IBM Co., Armonk, NY, USA). Between-group differences were compared using t-tests, and P values < 0.05 were considered significant.

Results

1. Monthly and annual meningitis frequency of patients
The monthly and annual number of pediatric meningitis in South Korea are reported in Supplementary Table 1. The monthly patient’s number peaked during the summer months (June, July, and August), with the highest number of cases registered in July. The total number of patients with meningitis and the major diagnosis of bacterial/viral meningitis correlated significantly during summer (P < 0.001), especially in July (Supplementary Fig. 1).
2. Age-stratified number & frequency of bacterial and viral meningitis

Bacterial meningitis was the most common type among infants; the number of cases in early childhood and that in adolescent age groups was similar (Fig. 2). When analyzing the number of patients against the total population, infants, neonates, childhood, and adolescence were in order. Viral meningitis was the most common in early/middle childhood (Fig. 3). Like bacterial meningitis, viral meningitis was in the same order when comparing the population by age group.

Table 1. Meningitis diagnostic codes in the Korean Standard Classification of Disease and Cause of Death (KCD-7)

<table>
<thead>
<tr>
<th>Diagnostic code</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial</strong></td>
<td></td>
</tr>
<tr>
<td>A170</td>
<td>Tuberculous meningitis, tuberculous leptomeningitis</td>
</tr>
<tr>
<td>A321</td>
<td>Listerial meningitis and meningoencephalitis, listerial meningitis</td>
</tr>
<tr>
<td>A390</td>
<td>Meningococcal meningitis</td>
</tr>
<tr>
<td>G00</td>
<td>Bacterial meningitis, bacterial leptomeningitis, bacterial meningitis, bacterial pachymeningitis</td>
</tr>
<tr>
<td>G000</td>
<td>Haemophilus meningitis, meningitis due to <em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td>G001</td>
<td>Pneumococcal meningitis</td>
</tr>
<tr>
<td>G002</td>
<td>Streptococcal meningitis</td>
</tr>
<tr>
<td>G003</td>
<td>Staphylococcal meningitis</td>
</tr>
<tr>
<td>G008</td>
<td>Bacterial meningitis associated with <em>Escherichia coli</em>, <em>Friedlander bacillus</em>, or <em>Klebsiella pneumoniae</em></td>
</tr>
<tr>
<td>G009</td>
<td>Bacterial, purulent, pyogenic, or suppurative meningitis</td>
</tr>
<tr>
<td>G01</td>
<td>Meningitis due to bacterial diseases classified elsewhere, including anthrax-, gonococcal-, and leptospirosis-related disease, among others</td>
</tr>
<tr>
<td><strong>Viral</strong></td>
<td></td>
</tr>
<tr>
<td>A87</td>
<td>Viral meningitis</td>
</tr>
<tr>
<td>A870</td>
<td>Enteroviral meningitis, coxsackievirus meningitis, echovirus meningitis</td>
</tr>
<tr>
<td>A871</td>
<td>Adenoviral meningitis</td>
</tr>
<tr>
<td>A872</td>
<td>Lymphocytic choriomeningitis</td>
</tr>
<tr>
<td>A878</td>
<td>Other viral meningitis</td>
</tr>
<tr>
<td>A879</td>
<td>Viral meningitis, unspecified</td>
</tr>
<tr>
<td>B003</td>
<td>Herpesviral meningitis</td>
</tr>
<tr>
<td>B010</td>
<td>Varicella meningitis</td>
</tr>
<tr>
<td>B021</td>
<td>Zoster meningitis</td>
</tr>
<tr>
<td>B051</td>
<td>Measles complicated by meningitis, post-measles meningitis</td>
</tr>
<tr>
<td>B060</td>
<td>Rubella meningitis</td>
</tr>
<tr>
<td>B261</td>
<td>Mumps meningitis</td>
</tr>
<tr>
<td>G020</td>
<td>Meningitis associated with viral diseases classified elsewhere (adenoviral, enteroviral, herpesviral, infectious mono, measles, mumps, rubella, varicella, zoster)</td>
</tr>
<tr>
<td>G030</td>
<td>Nonpyogenic meningitis, nonbacterial meningitis</td>
</tr>
<tr>
<td><strong>Fungal and parasitic</strong></td>
<td></td>
</tr>
<tr>
<td>B375</td>
<td>Candidal meningitis</td>
</tr>
<tr>
<td>B384</td>
<td>Coccidioidomycosis meningitis</td>
</tr>
<tr>
<td>B451</td>
<td>Cryptococcal meningitis</td>
</tr>
<tr>
<td>G021</td>
<td>Meningitis in mycoses, candidal, coccidioidomycosis, cryptococcal</td>
</tr>
<tr>
<td>G028</td>
<td>Meningitis associated with another infectious or parasitic diseases, including African trypanosomiasis and Chagas disease</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>G03</td>
<td>Meningitis due to unspecified cause, leptomeningitis due to other and unspecified causes, etc.</td>
</tr>
<tr>
<td>G031</td>
<td>Chronic meningitis</td>
</tr>
<tr>
<td>G032</td>
<td>Benign recurrent meningitis (Mollaret’s meningitis)</td>
</tr>
<tr>
<td>G038</td>
<td>Meningitis due to other specified causes</td>
</tr>
<tr>
<td>G039</td>
<td>Meningitis, unspecified</td>
</tr>
</tbody>
</table>

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3. Most common disease types

Among bacterial meningitis types, the total numbers of children registered with the disease codes G009 (bacterial, purulent, pyogenic, or suppurative meningitis), G008 (bacterial meningitis associated with *Escherichia coli*, Friedlander bacillus, or Klebsiella pneumonia), and G002 (streptococcal meningitis) were 1,261 (58.2%), 375 (17.3%), and 263 (12.1%), respectively. In addition, there were 79 cases (3.6%) of A170 (tuberculous meningitis, tuberculous leptomeningitis) disease, which was the most common in adolescence. Finally, among infants, there were 245 cases of G002, which made it more common than G008 (141 cases).

Among the different types of viral meningitis, A879 (viral meningitis, unspecified) was the most commonly reported diagnostic code (16,574 [45.8%]), followed by A870 (enteroviral meningitis, coxsackievirus meningitis, echovirus meningitis; 9,216 [25.5%]), G030 (nonpyogenic meningitis, nonbacterial meningitis; 4,648 [12.9%]), and A878 (other viral meningitis; 3,693 [10.2%]). Although the specific viral species were recorded in a small number of cases, most cases involved adolescents with mumps (B261), zoster (B021), herpes (B003), and enterovirus infections. Among infants, herpesviral meningitis was the most commonly reported type (Supplementary Table 2). In case of fungal meningitis, the disease code G028 (meningitis associated with another infectious or parasitic diseases, including African trypanosomiasis and Chagas disease) was the most commonly reported, although it involved relatively few cases among infants and a comparable num-

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**Fig. 1.** Protocol of data extraction for meningitis patients.

**Fig. 2.** (A) Bacterial and (B) viral meningitis by age group.

**Fig. 3.** Distribution of causes of (A) bacterial and (B) viral meningitis by age group.
number of cases across the remaining age groups.

4. Sex-stratified disease frequency

Overall, there was a higher frequency of meningitis among boys (1%) than girls (0.70%), based on the ratio of male-to-female patients in the overall sample (51,573 vs. 32,970) and that in the general population of Korea (data for children aged 0 to 17 years in 2010: boys vs. girls, 5,135,542 vs. 4,711,252).

In a large category, classified as bacterial and viral meningitis, there was higher frequency of bacterial meningitis among boys (0.024%) than girls (0.020%) (1,247 vs. 919). Similarly with bacterial meningitis, there was higher frequency of bacterial meningitis among boys (0.43%) than girls (0.30%) (21,904 vs. 14,251).

Discussion

The present study investigated the data of bacterial and viral meningitis obtained from the Korean HIRA database to identify the temporal- and sex-related trends in the frequency of all-cause meningitis in children. In previous studies analyzing outbreaks from the late 90s to the early 2000s have shown that the most common meningitis-related pathogens were group B Streptococcus (GBS), Streptococcus pneumoniae, and H. influenzae [14,15]. Although the result is a single medical institution or several medical institutions, it can be considered a significant result.

A United States-based report on the etiology of bacterial meningitis during 1998 to 2007 revealed that GBS, Listeria monocytogenes, and S. pneumoniae were the predominant pathogens causing meningitis among patients aged < 2 months. Among children aged between 2 months and 2 years, S. pneumoniae, GBS, Neisseria meningitidis, and H. influenzae were the common cause of meningitis, while among children aged 2 to 17 years, S. pneumoniae, N. meningitidis, and H. influenzae were the most common causative agents [19,20].

A global meta-analysis that investigated meningitis etiology revealed S. pneumoniae as the most common cause of the disease among children. In Europe, meningitis due to N. meningitidis was the most prevalent among children aged 1 to 5 years, whereas that caused by E. coli and S. pneumoniae were the most prevalent among African neonates. Moreover, neonates in Europe had the highest prevalence of GBS infection, which was rare in the Eastern Mediterranean region [6]. Overall, the reported frequency differs between regions.

In the present study, the broadest diagnostic category corresponded to the disease code G009; several other diagnostic entities were included, and G008 included E. coli infections. Among cases in which the pathogen was identified, streptococcal meningitis was the most common among infants, which was consistent with domestic epidemiology.

Many H. influenzae outbreaks have been reported previously [14,15]; however, there have been relatively few outbreaks in the last 10 years. Of note, the code A170 appeared more than the other diagnostic names in adolescence, which may be due to the higher overall prevalence of tuberculosis in Korea [21]. However, pathogens that belong to the disease code G000 (Table 1), associated with H. influenzae (which used to be common), were rarely reported in the present study. This finding might be accounted for by the introduction of a national immunization support program for children (eight types) in 2009, with an additional anti-Hib vaccination administered since 2013 [22].

Immunization of children is effective for disease prevention worldwide. From 2000 to 2015 in particular, the frequency and mortality rates of meningitis due to S. pneumoniae and type B H. influenzae were reduced following the active implementation of conjugate vaccines worldwide [23,24]. In addition, in Japan, which shares climate and infectious disease characteristics with Korea, a recent study has shown that the frequency of bacterial meningitis has been decreasing since the last several years owing to increased vaccinations against H. influenzae and S. pneumoniae [25]. This finding is considered statistically significant and is consistent with trends observed elsewhere.

The enterovirus family is the leading cause of viral meningitis, followed by mumps and herpes simplex virus [10,26,27]. Mumps commonly occurs in adolescent children, whereas herpessviral and varicella-zoster virus meningitis tend to present among infants; these findings are consistent with those previously published in Korea [12,27,28].

The age-dependent frequency rate showed that viral meningitis was equally likely to occur across all age groups; however, bacterial meningitis was most likely to occur in infants [9,10,12,29,30]. Both types of meningitis were most likely to occur during the summer season, particularly in July. Viral meningitis was strongly associated with enterovirus infection, which is prevalent during summers. The frequency of bacterial meningitis followed a similar seasonal pattern [26,30-32]. This finding is likely due to the fact that bacteria such as E. coli or Klebsiella spp. (associated with the G008 diagnostic code), which account for a large proportion of bacterial meningitis cases, show an increased survival rate (by 3.5% to 8%) with a temperature increase by 5.6°C.

Owing to the large influence of temperature, infections during summer seemed to occur more vigorously than during winter [33,34]. The major strength of this study is its use of a large-scale database derived from health insurance claims, which allowed us to examine meningitis frequencies in detail. However, this study has
some limitations. First, since the diagnosis recorded in the database is based on KCD-7 codes, diagnostic details relevant to meningitis (e.g., type of pathogen) were often unavailable. There is a disadvantage in using statistics to identify bacteria or viruses that cause a specific outbreak. For example, even if *E. coli* is detected, it is difficult to evaluate all the causes of the outbreak because the diagnosis code G008 (Other bacterial meningitis; due to *E. coli*, *P. bacillus*, *Klebsiella*) includes infection caused by all related bacteria, without detailed diagnosis.

Second, a diagnostic code such as G039 (meningitis, unspecified) corresponding to other diagnostic names may be clearly detected as meningitis in a medical institution, but unspecified diagnostic names may only reflect clinical symptoms. To maximally exclude these errors, only the data of patients who were admitted to the hospital were extracted; however, this error cannot be avoided.

Third, as our data source only included the data of the main diagnosis, cases involving meningitis that progressed to other diseases (e.g., sepsis) might have been missed.

In summary, this study examined meningitis frequency data using population-wide information derived from a medical insurance claims database. Further studies are required to elucidate the relationship between meningitis and other infectious diseases, including ones with analyses that address the current study limitations. Taken together, this evidence will contribute toward a better understanding of childhood meningitis in Korea.

Supplementary materials

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Conflicts of interest

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

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Hyperkinesia after High-Dose Prednisolone Therapy in a Patient with West Syndrome

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West syndrome is the most common developmental and epileptic encephalopathy in infancy and is characterized by clinical spasms, hypsarrhythmia on electroencephalogram (EEG), and developmental regression. Despite the accumulation of discoveries of genetic causes, steroids and vigabatrin (VGB) remain as the first-line treatments because they are more effective than other available therapies [1]. Due to the risk of treatment failure with VGB or hormonal therapy alone and the grave consequences of delayed treatment, instead of choosing either VGB or hormonal therapy, the literature increasingly supports the combination of VGB and hormonal therapy as the initial treatment for West syndrome [2].

However, adverse effects of corticosteroids and VGB are important factors to take into consideration when treating patients with West syndrome. Potential serious adverse effects of hormonal therapies include immunosuppression, hypertension, hypokalemia, adrenal or pituitary insufficiency, and gastrointestinal bleeding [2]. Adverse effects of VGB include permanent defects of the bilateral concentric peripheral visual field and magnetic resonance imaging (MRI) toxicity presenting as a reversible high T2 signal and restricted diffusion in the thalamus, basal ganglia, brainstem tegmentum, and cerebellar dentate nucleus which often occur in association with hyperkinetic movement disorders [2].

Here, we report the case of a patient receiving VGB and high-dose oral prednisolone combination therapy who presented with hyperkinetic dyskinesia, which was potentially attributed to the adverse effects of high-dose prednisolone rather than VGB. This study was approved by the Institutional Review Board of Pusan National University Yangsan Hospital (05-2020-403). Informed consent was obtained from the parent of the patient.

An 8-month-old girl who had been treated for West syndrome with VGB and high-dose prednisolone add-on therapy presented to the clinic with hyperkinesia that started 4 days earlier. The patient adhered to the following protocol for VGB and high-dose prednisolone add-on therapy: 50 mg/kg/day VGB on day 1, 100 mg/kg/day VGB on days 2–4, 150 mg/kg/day VGB on days 5–13, 150 mg/kg/day VGB+40 mg/day prednisolone on days 14–20, 150 mg/kg/day VGB+60 mg/day prednisolone on days 21–27. The dosages or increments were to be altered if the spasms or EEG hypsarrhythmia persisted. After the treatment protocol, the prednisolone dosage was to be tapered over the following 15 days, while the VGB dosage was to be maintained for 5 months and then tapered over 1
The hyperkinetic movement started when the patient was on the 7th day of 60 mg prednisolone. It first started as intermittent shaking of the hands, which soon included occasional shaking of the head, followed by nearly continuous shaking of the whole body while conscious, making it difficult for her to drink milk from the bottle. The hyperkinetic movement showed oscillating large amplitude tremor-like appearance which appeared at rest or during movement. There were no identifiable triggering factors, but the hyperkinetic movements disappeared during sleep (Supplementary Video 1).

She had been diagnosed with West syndrome of an unknown etiology, with no brain MRI abnormalities and negative results for an epilepsy gene panel. She had shown normal development before the onset of West syndrome, and regressed since—she cannot contact her eyes, and can barely control her head. She had been seizure free since the administration of 60 mg of prednisolone, despite constant drowsiness. The physical examination results including pupil reflexes and deep tendon reflexes, as well as routine laboratory results including blood chemistry, glucose, and electrolytes were normal. Her EEG did not show any changes since her last exam, which was 4 days earlier. The hyperkinetic movement did not accompany any ictal changes, and her brain MRI was normal without any signs of VGB-related toxicity. Because prednisolone treatment exhibited a potential temporal causal relationship and was therefore more likely the source of the adverse effects, we tapered off the prednisolone while providing nutritional support via a nasogastric tube. The abnormal movement started to improve 2 days after discontinuation of prednisolone and completely disappeared after 5 days. The patient also gained alertness at this time.

It is well known that patients receiving VGB can show reversible MRI lesions, as described above [4]. However, whether those lesions are the true cause of abnormal movements, such as those observed in West syndrome patients receiving treatment, remains unclear. MRI changes associated with VGB are not specifically related to movement disorders, and patients often show improvement without a dose reduction of VGB or no improvement after discontinuation of VGB [4]. Also, in clinical trials evaluating VGB and corticosteroid combination therapy, the incidence rates of abnormal movements and drowsiness have been as high as 8% and 24%, respectively, suggesting that corticosteroids may partially contribute to the dyskinesia and drowsiness or increase the susceptibility to VGB toxicity [2].

Our patient showed hyperkinesia during combination therapy, which soon stopped after the discontinuation of prednisolone. She continued with 150 mg/kg/day of VGB over the following 5 months without any signs of hyperkinesia. To the authors’ knowledge, there is only one report on a series of patients showing dyskinesia after hormonal treatment [5]. However, movement disorders are inconsistently related to VGB toxicity, and there is an increased incidence of movement disorders in patients receiving combination therapy than those receiving monotherapy [2,4]. Therefore, prednisolone may directly or indirectly attribute to movement disorders. However, the pathological mechanism of this phenomenon warrants further investigation.

Supplementary Material

Supplementary materials related to this article can be found online at https://doi.org/10.26815/acn.2020.00248.

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Mirror Movements (MMs) refer to involuntary movements in one limb that are performed simultaneously with voluntary movements in the other limb [1-4]. Although MMs are observed in normal children aged < 10 years when the corpus callosum is maturing, pathological MMs may be noted in patients who have experienced cerebral infarction, Parkinson’s disease, tumors, or vertebral trauma [1-4]. Here, we report a 9-year-old boy with a germinoma in the right basal ganglia presenting with only MMs in the ipsilateral hand without other neurological problems.

A 9-year-old boy experienced difficulties in performing bimanual tasks, such as playing the piano and computer games, owing to involuntary movements of his right hand that had been first observed 3 months earlier. Prior to the onset of such movements, he had been healthy; his birth had been uneventful. He was born to non-consanguineous parents at a gestational age of 40 weeks with a birth weight of 3.92 kg. None of the family members presented with similar MMs or other neurological disorders. A neurological examination revealed no paresis or paresthesia. However, recurrent fisting of his left hand caused involuntary and clumsy fisting of his right hand.

The findings of other physical examinations, basic laboratory tests, chest roentgenography, and electrocardiography were all normal. Brain magnetic resonance imaging (MRI) performed on admission revealed a mass measuring 4.8 × 3.2 cm, with mixed cystic and solid components, in the right basal ganglia (Fig. 1A-D). Brain tractography image revealed disruption and posterior displacement of the fibers of the right corticospinal tract in the right frontal lobe; however, aberrant projections were not observed (Fig. 1E and F). Biopsy and pathological evaluation of the tissue from the brain lesion revealed that the lesion was populated by large tumor cells with clear cytoplasm and occasional distinct nucleoli (Fig. 2A). The tumor cells were interspersed with mature lymphocytes. The tumor cells were strongly positive for placental alkaline phosphatase and CD117 (c-Kit) in the immunohistochemical analysis (Fig. 2B). The lesion was diagnosed as a germinoma. The level of serum beta-human chorionic gonadotropin (β-hCG) was 61 mIU/mL (normal range, 0 to 5). No metastatic lesion was found on whole-spine MRI.

The patient received Korean Society for Pediatric Neuro-Oncology 081 (KSPNO 081) chemotherapy. During chemotherapy, the patient could perform bimanual tasks more comfortably.
Fig. 1. Brain magnetic resonance imaging (MRI) was initially performed for diagnosis (A-F) and 3 months after the first visit (G, H). Axial T1-weighted (A) and axial T2-weighted (B) images showing multiple cystic and solid masses with perilesional edema in the right basal ganglia. Axial (C) and sagittal (D) contrast-enhanced T1-weighted images showing enhancement in the cystic walls and solid portions. Diffusion-tensor images (E, F) showing disruption and posterior displacement of fibers of the right corticospinal tract in the right frontal lobe. The axial T2-weighted (G) and T1-weighted (H) contrast-enhanced images showing decreased tumor spread and decreased enhancement and cystic components.

Fig. 2. Histopathological findings for the germinoma. (A) The lesion comprises large tumor cells with clear cytoplasm and mature lymphocytes (hematoxylin and eosin staining, ×200). (B) The tumor cells are immunoreactive for placental alkaline phosphatase (immunohistochemical staining, ×200).

with the gradual alleviation of the MMs in his right hand. At the end of chemotherapy, the serum β-hCG levels had decreased to 2 mIU/mL. The second brain MRI performed 3 months after the first visit showed a decrease in the spread of the tumor in the right basal ganglia (3.4 × 3.2 cm) and decreased enhancement and cystic components (Fig. 1G and H). The patient received radiotherapy at 1 month after the termination of chemotherapy. The MMs were still observed intermittently in his right hand, although they were mild.

A germinoma can develop in the pineal recess, suprasellar region, basal ganglia, and thalamus, and it can be associated with increased levels of β-hCG in the serum and cerebrospinal fluid [5]. The main treatment strategies for this tumor are radiotherapy and pre-radiation chemotherapy [5]. Patients with intracranial germi-
nomas can present various symptoms, such as diabetes insipidus, growth retardation, precocious puberty, headache, visual disturbance, gait abnormalities, and motor weakness [5]. Involuntary movements, such as dystonia and choreoathetosis, have been reported in only a few patients with germinomas [5].

Pathological MMs without underlying structural abnormalities or specific syndromes (e.g., Klippel-Feil syndrome, Kallmann syndrome, agenesis of the corpus callosum, Arnold-Chiari malformation, or cleft spine) are associated with haploinsufficiency of some causative genes, namely, DCC, RAD51, and netrin-1 [1,2]. Late-onset MMs are associated with degenerative or acquired diseases or trauma, such as Parkinson’s disease, cerebrovascular diseases, craniovertebral damage, or (very rarely) brain tumors [1-4]. The brain lesions associated with late-onset MMs mostly involve the corpus callosum and primary motor cortex (M1) and occasionally secondary motor areas (e.g., the supplementary motor cortex, dorsal premotor cortex, and basal ganglia) [1-4].

Three hypotheses have been proposed for the development of MMs. Per the first hypothesis, MM develops owing to the abnormal development or decussation of the corticospinal tract (mainly in the medulla or at the upper cervical level). The second hypothesis states that MM develops owing to the imbalanced interhemispheric inhibition concomitant with bilateral activation of the M1. The third hypothesis is that MM develops owing to the abnormal bilateral delivery of signals to the M1 from the secondary motor areas [1,2]. None of these hypotheses have been confirmed; however, the first two hypotheses are commonly reported [1-4].

The loss of interhemispheric inhibition, which leads to the development of MMs, is identified in patients with defects of the corpus callosum (e.g., agenesis/dysgenesis, traumatic damage, or tumor invasion) or lesions in M1 such as infarction, trauma, or tumor [1-4]. Kaulen and Baehring [3] described a patient with MMs in the contralateral hand owing to a scar or residual tumor in the right corpus callosum and corona radiata at 1 year after right frontoparietal oligoastrocytoma surgery. In this patient, the development of MMs was attributed to the loss of interhemispheric inhibitory input to the ipsilateral M1 via the damaged areas of the ipsilateral corpus callosum [3].

Concomitant bilateral facilitation of the M1 owing to abnormally delivered signals from the secondary motor areas has been recognized in a few patients with MMs [1]. This mechanism may also apply in our case. In our case, the germinoma in the right basal ganglia may have activated the contralateral M1 in response to ipsilateral M1 activation. Therefore, our case was characterized by MMs in the ipsilateral hand concomitant with a right basal ganglia germinoma. Unfortunately, this hypothesis could not be proved in our case as functional brain MRI scans were not available for our patient.

To the best of our knowledge, this is the first case of a brain tumor presenting with only MMs, and is a rare report of MMs associated with the unilateral basal ganglia lesion.

Informed consent was waived by the Institutional Review Board of Chonnam National University Hospital (CNUH-EXP-2020-296) due to a retrospective nature of our study.

Conflicts of interest

Young Ok Kim is an editorial board member of the journal, but she was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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The voltage-gated sodium channel, type II, alpha (SCN2A) gene (OMIM 182390) encodes the alpha subunit of Na\(^{+}\)\(_{\text{v}}\)1.2 [1]. It is expressed plentifully in neurons during early infancy and plays a role in neuronal excitability [2]. SCN2A variants are one of the causes of neurodevelopmental disorders, accounting for 1% of all epileptic encephalopathies [3].

There are several epilepsy phenotypes associated with SCN2A variants: benign familial neonatal-infantile seizures, neonatal seizures and late onset episodic ataxia, developmental epileptic encephalopathy, and autism spectrum disorders. In addition, there are many seizure types associated with SCN2A variants, including focal clonic seizures, focal tonic seizures, generalized tonic clonic seizures, hemi-clonic seizures, spasms, myoclonic seizures, and atonic seizures [4]. The phenotypic variability associated with SCN2A variants has been reported in the review of literatures [3,4]. The location of the variants and functional effects on protein can contribute to the clinical phenotypes; however, the correlation between genotype and phenotype has not been revealed clearly [4].

With the remarkable advancements in molecular genetic technologies in recent decades, various genetic testing methods have been developed to elucidate the genetic cause of epilepsy. High-throughput nucleotide sequencing is one of the most useful diagnostic tools because of its cost-effectiveness and high diagnostic yield in patients with early onset epilepsy. This tool has saved time and expense in the diagnosis of genetic causes in genetic epilepsy patients with highly heterogeneous phenotypes [5].

We report a case of SCN2A pathogenic variant in a developmental epileptic encephalopathy patient who was successfully treated with an adequate anti-seizure medication through the epilepsy gene panel testing based on high-throughput nucleotide sequencing method. This study was approved by the Institutional Review Board of Samsung Seoul Hospital (IRB No. 2014-07-001-004 and 2019-01-030). Written informed consent by the patients was waived due to a retrospective nature of our study.

A male neonate born at 38\(^{+1}\) weeks of gestation was referred to another neonatal intensive care unit with seizures that had begun on the day of birth. He was the second baby of the family and was born by vaginal delivery. After birth, he was treated with oxygen with meconium aspiration for several hours. He had no family history.
of neuromuscular, metabolic, or genetic disorders. His weight, height, and head circumference were 2,900 g (25–75th percentile), 49 cm (50–75th percentile), and 35 cm (75–90th percentile), respectively. He showed generalized tonic seizures 15 hours after birth and was evaluated for electrolytes, brain ultrasonography, cerebrospinal fluid analysis, and metabolic abnormalities, all of which were normal. He was then treated with three doses of intravenous phenobarbital (each 10 mg/kg). Brain magnetic resonance imaging was normal, and repeated blood tests including electrolytes, ammonia, and metabolic analysis were normal.

He was transferred to this institution on the 4th day after birth. On admission, he showed a mildly hypotonic posture although sucking power was good. There were no anomalies or remarkable findings without caput succedaneum in the vertex area. Neurological examination was normal, and primitive reflexes such as the Moro reflex, sucking reflex, and rooting reflex were present. The initial electroencephalography on arrival revealed multifocal spike or polyspike discharges from the left or right temporal, central, or occipital areas and showed intermittent background suppression lasting about 2 to 5 seconds (Fig. 1A and B). There were frequent electro-clinical or electroencephalographic seizures arising from the left temporal areas lasting about 20 to 40 seconds (Fig. 1C). After administration of pyridoxine and levetiracetam (20 mg/kg, three times), the clinical seizures disappeared. However, electroencephalographic seizures appeared intermittently and were managed with further doses of levetiracetam. On the 7th day in the hospital, the epilepsy gene panel testing based on high-throughput nucleotide sequencing method was performed because there was no remarkable cause found with brain magnetic resonance imaging and metabolic disease screening test. For the intractable seizures, the patient was treated with adding topiramate and a ketogenic diet. After administration of oxcarbazepine on the 30th day in the hospital, the seizures had been controlled clinically and electroencephalographically. However, the electroencephalography showed frequent spike discharges from the left or right temporal or central areas. He was discharged on the 40th day from the hospital after being seizure free for 9 days with multiple anti-seizure medications (phenobarbital, phenytoin, levetiracetam, topiramate, oxcarbazepine, and pyridoxine). After a week, the gene panel testing revealed a pathogenic variant of the SCN2A gene (NM_021007.2: c.4609A>T; p.(Ile537Phe), heterozygous variant), which was found to be de novo after analysis of the parents’ DNA. After dis-
charge, the patient showed focal motor seizures lasting about 10 to 70 seconds with a frequency of 2 to 14 times daily. The doses of phenytoin and oxcarbazepine were increased based on the results of the gene panel testing. On the 61st day after birth (19 days after discharge), he became completely seizure free after the phenytoin (25 mg three times a day, 14 mg/kg/day, serum trough level = 12.37 µg/mL) and oxcarbazepine (120 mg twice a day, 46.2 mg/kg/day, serum trough level of 10-hydroxy-carbazepine = 8.6 mg/L, therapeutic range: 3 to 35 mg/L) dosages were adjusted. Occasionally, he showed break-through seizures, which became under control with adjusting the dose of phenytoin. At the age of 27 months, he showed clustering seizures during a febrile illness associated with respiratory syncytial virus infection. At that time, he couldn’t take the anti-seizure medication with gastroenteritis associated with viral illness. His seizures were controlled with intravenous administration of phenytoin and his electroencephalography was normal (Fig. 1D). Because the effects of phenytoin and oxcarbazepine were insufficient to control his seizures, we added carbamazepine (150 mg twice a day, 21.7 mg/kg/day, serum trough level = 2.9 µg/mL), another sodium channel blocker, after his vomiting and fever subsided. The clinical course was summarized in Fig. 2.

In the last clinical follow-up, he was a 3-year-old and has been seizure free with three anti-seizure medications (carbamazepine, oxcarbazepine, and phenytoin). He showed global developmental delay, could stand with assistance, walk with full assist, express several vowel sounds, and understand several orders such as ‘point to your nose.’

In a large cohort study of 201 patients with SCN2A-related disorders, developmental epileptic encephalopathy with early onset before the age of 3 months accounted for 36% (n = 37). Most of them (n = 31) showed their first seizure within a week like our case and their clinical manifestations had a wide range of epilepsy syndromes. The response to sodium channel blockers was very different for each patient. Among sodium channel blockers, phenytoin was the most effective anti-seizure medication. There were eight patients being seizure free with phenytoin and our patient also showed good response to intravenous administration of phenytoin [3].

We report a case of SCN2A pathogenic variant treated with an adequate anti-seizure medication based on the findings of high-throughput nucleotide sequencing-based gene panel testing.

Conflicts of interest

Jeehun Lee is an editorial board member of the journal, but he was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.
Author contribution

Conceptualization: JL and JL. Data curation: DL, JYS, and JL. Formal analysis: DL and JYS. Methodology: SEP, DL, and JL. Project administration: JL. Writing-original draft: SEP and JL. Writing-review & editing: JL and JL.

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Autosomal-dominant hypocalcemia with hypercalciuria (ADHH) is a genetic disease characterized by hypoparathyroidism, hypocalcemia, and varying degrees of hypocalcemia. Although convulsions can occur with hypocalcemia, most patients are asymptomatic or show intermittent limb numbness, muscular contractions, and laryngeal spasms [1]. Most patients with ADHH have a missense mutation in the calcium sensing receptor (CASR) gene [1]. CaSR is a 1078-residue glycoprotein, encoded by six exons of CASR located on chromosome 3q13.3-21, and is primarily expressed in the parathyroid gland and renal tubules [2]. It plays a pivotal role in systemic calcium metabolism by regulating parathyroid hormone secretion and urinary calcium excretion [3]. Dysfunctions in the CaSR manifest differentially, depending on the locus of the mutation, or mutations in other CASR-associated genes [3].

Here, we report a case of ADHH as confirmed by whole exome sequencing (WES). A 9-year-old boy reported with frequent repetitive generalized tonic-clonic seizures over a course of 2 months. The seizures occurred spontaneously, lasting for 5 to 60 seconds, followed by urination and decreased muscle tone. He was born via cesarean section at 36 weeks gestation with a birth weight of 3.4 kg (94th percentile), and was subsequently admitted to the neonatal intensive care unit with hypoxia. Following discharge, he survived normally without any abnormal neurological symptoms. His mother had mild tingling sensations in her limbs, but was never diagnosed with any neurological conditions. At the first hospital visit, his body weight, height, and head circumference were 43.2 kg (86th percentile), 143.7 cm (82th percentile), and 56 cm (96th percentile), respectively. He had no physical defects or deformities. His initial vital signs were within the normal ranges, and neurologic examination was unremarkable. Upon laboratory testing, hypocalcemia (6.6 mg/dL; reference range, 8.6 to 10.2) and hyperphosphatemia (8.8 mg/dL; reference range, 2.0 to 5.5) with borderline hypercalciuria (urine calcium/creatinine ratio: 0.198; reference range, 0 to 0.2) were found without evidence of severe vitamin D deficiency (25-hydroxy-vitamin D: 25.57 ng/mL; reference range, 30 to 100). The serum levels of parathyroid hormone (PTH-I) dropped to 13.91 pg/mL (reference range, 15 to 65). Interictal electro-
encephalography (EEG) showed semi-rhythmic high amplitude 3 to 4 Hz delta frequency activity from the left fronto-temporal area following hyperventilation. Under the initial impression of hypoparathyroidism, oral calcium preparations (40 mg/kg/day as elemental calcium) and alfacalcidol (12 ng/kg/day) were prescribed. His serum calcium levels recovered, and were within the normal range. A year later, the patient revisited the hospital because the frequency of convulsions that had previously decreased with medica-
tion, had increased. His serum calcium levels dropped to 6.8 mg/dL despite high-dose calcium treatment. Intravenous calcium gluconate and high-dose vitamin D were injected, but refractory hypocalcemia with generalized seizures persisted. Brain computed tomography (CT) revealed multiple gross calcifications in the bilateral cerebral white matter, basal ganglia, thalamus, and cerebellum (Fig. 1A and B). A kidney stone was found on abdominopelvic CT scan (Fig. 1C). WES was performed for elucidating the exact

Fig. 1. (A, B) Multiple calcifications (white areas) are observed in the basal ganglia and frontal white matter in the cross sectional view on brain computed tomography. (C) A small kidney stone is evident in the left kidney (arrow).

Fig. 2. The serial progress in the serum levels of calcium, phosphorus, and parathyroid hormone (PTH-I), and the doses of the medications. PO, per os.
cause of the symptoms, which revealed a likely pathogenic [4] heterozygous missense mutation in the CASR gene (c.721G > A [p. Glu241Lys]). Trio-WES was performed on the parents, and the same mutation was found in his mother. Blood tests were subsequently performed on his mother, and her serum levels of calcium and PTH-I were 6.6 mg/dL and 12.38 pg/mL, respectively, indicating hypocalcemic hypoparathyroidism like the patient. The frequency of hypocalcemic seizures gradually decreased following treatment with increasing doses of calcitriol and calcium carbonate and the addition of 0.5 mg/kg/day hydrochlorothiazide. After 5 months, the patient was re-admitted with abrupt hypercalcemia. The levels of blood calcium and ionized calcium were 13.5 mg/dL and 1.68 mmol/L, respectively, despite steadily decreasing doses of oral calcium supplementation. After the doses of calcium and vitamin D were further reduced, the blood calcium levels gradually returned to the normal range. An EEG after 16 months revealed no epileptic discharges. Three years post diagnosis, the patient was still taking calcitriol (5 ng/kg/day) and calcium carbonate (8 mg/kg/day as elemental calcium), and did not have tingling sensations or seizures. The serial progression in the serum levels of calcium, phosphorus, and PTH-I, and dose of the medications are schematically presented in Fig. 2.

The common clinical symptoms of patients with hypoparathyroidism range from asymptomatic to severe symptomatic hypocalcemia. However, in this case, the clinical manifestations of a missense mutation in the CASR gene (c.721G > A [p.Glu241Lys]) had more diverse effects on the serum calcium levels, ranging from refractory hypocalcemia to hypercalcemia during long-term follow-up. Hyperparathyroidism or hypoparathyroidism may appear depending on the locus of the mutation. However, Hannan et al. [4] reported that both hypocalcemia and hypercalcemia can occur due to a p.Glu250Lys mutation in CASR. Similarly, the calcium levels in our patient remained normal for a while, for which the administration of calcium was gradually reduced. However, the patient suddenly developed severe hypercalcemia. Notably, the p.Glu241Lys mutation identified herein also caused severe hypercalcemia when the calcium replacement was tapered. During the 3 years of follow-up, the p.Glu241Lys mutation in CASR responded poorly to calcium or vitamin D modulation therapy and showed periodic dysregulated pendular hypocalcemia and hypercalcemia.

ADHH patients with hypocalcemic convulsions are commonly treated with parenteral calcium for increasing serum calcium, followed by maintenance with oral calcium and vitamin D supplementation. However, calcium treatments should be limited to hypocalcemic or symptomatic conditions, as nephrocalcinosis may occur as a side effect. Thiazides can be used for reducing the amount of excreted urinary calcium. The serum and urine calcium concentrations should be checked every 3 to 6 months for re-determining the appropriate dose of the drug [3]. In this case, severe hypercalcemia followed by hypercalcemia occurred within 5 months, despite regular checkups for calcium concentration and treatment modulation.

In conclusion, we report a case of a p.Glu241Lys mutation in CASR, as detected by WES, in which the serum calcium levels varied periodically between severe hypocalcemia with refractory generalized seizures and unexpected hypercalcemia during long-term follow-up. This is the first report of a p.Glu241Lys mutation in CASR, with phenotypes of hypocalcemia and hypercalcemia, and insignificant responses to medical treatment. This mutation induces sudden irregular changes in the calcium concentration, making treatment difficult and requiring frequent serum calcium tests and detailed drug concentrations for controlling treatment.

This study was approved by the Institutional Review Board of CHA Bundang Medical Center (IRB No: 2018-06-008). Written informed consent was obtained from all patients.

Conflicts of interest

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

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3. Vahe C, Benomar K, Espiard S, Coppin L, Jannin A, Odou MF,

Acute necrotizing encephalopathy (ANE) of childhood is characterized by encephalopathy presenting with symmetrical multiple necrotic brain lesions along with multiple organ involvement. Affected children often present dramatic and profound neurologic deficits after prodromal viral infection symptoms. We report a case of a 4-year-old boy with acute necrotizing encephalitis related to *Mycoplasma pneumoniae* who managed to recover from severe neurocognitive impairment. A previously healthy 4-year-old boy had traveled around America and Spain for 1 month. Ten days after return, he had fever due to acute pharyngotonsillitis. On the third day of fever, he experienced abdominal pain, vomiting, and a generalized tonic seizure. He was transferred to the emergency room with an ongoing seizure of 30 minutes which ceased after injection of lorazepam.

The patient was drowsy but cranial nerve exam, pupillary light reflex, and extraocular movements were normal. Overall motor and sensory function was intact. Within 2 hours of admission the patient had three vomiting episodes. The initial diffusion-weighted brain magnetic resonance imaging (MRI) showed no diffusion-restriction lesions and the intrathecal pressure was normal. Blood and cerebrospinal fluid (CSF) tests, renal parameters, electrolyte levels, and urine analysis were also normal. Chest radiograph showed mild bilateral peribronchial infiltrations. The patient was then admitted to the intensive care unit. Next morning, his Glasgow coma scale (GCS) was 6 (eye opening 1, verbal response 2, and motor response 3). He showed generalized rigidity of extremities and no response to pain. Intubation was done to obtain respiratory stability. Clinically suspecting encephalitis, intravenous immunoglobulins (IVIG; 500 mg/kg/day, for 5 days) and high-dose methylprednisolone pulse therapy (30 mg/kg/day, for 3 days) were immediately started. Repeated brain MRI showed symmetric diffusion restriction and T2 high-signal intensity at both thalami. Inside the thalamus, the gradient recall echo showed low-signal intensity, indicating possible hemorrhagic lesions. Abrupt changes were seen in less than a day, which gradually resolved (Fig. 1). We diagnosed him with ANE.

Acute necrotizing encephalopathy (ANE) of childhood is characterized by encephalopathy presenting with symmetrical multiple necrotic brain lesions along with multiple organ involvement. Affected children often present dramatic and profound neurologic deficits after prodromal viral infection symptoms. We report a case of a 4-year-old boy with acute necrotizing encephalitis related to *Mycoplasma pneumoniae* who managed to recover from severe neurocognitive impairment. A previously healthy 4-year-old boy had traveled around America and Spain for 1 month. Ten days after return, he had fever due to acute pharyngotonsillitis. On the third day of fever, he experienced abdominal pain, vomiting, and a generalized tonic seizure. He was transferred to the emergency room with an on-going seizure of 30 minutes which ceased after injection of lorazepam.

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Empirical cefotaxime, vancomycin, and acyclovir were administered. Following the general tonic seizure on the second day, the patient had five consecutive seizure episodes. Fosphenytoin and levetiracetam were administered. Continuous electro-encephalography showed delta waves on background exhibiting nonspecific diffuse cortical dysfunction, but no epileptiform discharges.

The CSF culture, viral and bacterial multiplex
polymerase chain reaction (PCR) tests were negative. Real-time PCR from nasopharyngeal swab was negative for human adenovirus, bocavirus, coronavirus, enterovirus, influenza A/B, metapneumovirus, parainfluenza virus, rhinovirus, and respiratory syncytial virus. Serologic tests for herpes simplex virus, mumps virus, Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, and Japanese encephalitis virus were all negative except for M. pneumoniae. The immunoglobulin M (IgM) titer of M. pneumoniae on hospital day 1 was 416.89 U/mL (cutoff level, 71 U/mL), which fell to 363.98 U/mL on day 11 and 54.11 U/mL on the 8-month follow-up. Stool culture, viral and bacterial panel results were also negative. Empirical cefotaxime and vancomycin were switched to azithromycin.

For 4 days, the patient maintained a GCS score between 5 and 6 and required mechanical ventilation. On hospital day 5, his GCS score recovered to 10 (spontaneous eye opening 4, comprehensible sounds 2, withdrawal response to pain 4). On hospital day 43 at discharge, his motor power of upper extremities had recovered to grade 3 and lower extremities to grade 2. Sensory functions were not testable. He had grade 3 deep tendon reflexes, and all four limbs showed some rigidity. He could comprehend spoken words but had difficulty in expressing himself. All the results from whole exome study including pore protein ran binding protein 2 (RANBP2) gene, recently known for its correlation with familial autosomal dominant ANE [1] were normal. On last follow-up at 8 months, he had recovered fully in all developmental domains, except for gait disturbance and generalized intentional tremor predominant on the left side. Dyskinesia, slow speech, and tremor were improved by levodopa. Subsequent brain MRI on day 197 showed resolution of the ANE.

![Fig. 1.](https://doi.org/10.26815/acn.2020.00185)

<table>
<thead>
<tr>
<th>Day 1</th>
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<th>Day 9</th>
<th>Day 197</th>
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<td><img src="image11.png" alt="K" /></td>
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<td><img src="image14.png" alt="N" /></td>
<td><img src="image15.png" alt="O" /></td>
<td><img src="image16.png" alt="P" /></td>
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</tbody>
</table>

For 4 days, the patient maintained a GCS score between 5 and 6 and required mechanical ventilation. On hospital day 5, his GCS score recovered to 10 (spontaneous eye opening 4, comprehensible sounds 2, withdrawal response to pain 4). On hospital day 43 at discharge, his motor power of upper extremities had recovered to grade 3 and lower extremities to grade 2. Sensory functions were not testable. He had grade 3 deep tendon reflexes, and all four limbs showed some rigidity. He could comprehend spoken words but had difficulty in expressing himself. All the results from whole exome study including pore protein ran binding protein 2 (RANBP2) gene, recently known for its correlation with familial autosomal dominant ANE [1] were normal. On last follow-up at 8 months, he had recovered fully in all developmental domains, except for gait disturbance and generalized intentional tremor predominant on the left side. Dyskinesia, slow speech, and tremor were improved by levodopa. Subsequent brain MRI on day 197 showed resolution of the ANE.
The ANE is generally thought to occur via three main mechanisms: direct neuroinvasion, neurotoxin, and most of all, infection leading to immune dysfunction [2]. Typically, a viral or bacterial infection precedes ANE. *M. pneumoniae* can also lead to extrapulmonary manifestations including central nervous system (CNS) complications. In a study of 1,988 patients in the California Encephalitis Project, *M. pneumoniae* was the most common agent implicated in encephalitis, especially in children [3]. They were diagnosed primarily by the elevation of *M. pneumoniae* IgM in the blood. PCR and antibodies in CSF were rarely positive [3]. Qualitative measurement of IgM has only moderate sensitivity, but serial testing in our patient revealed peak levels at hospital day 1 and then a gradual decrease which turned to negative after 8 months, strongly implying that *M. pneumoniae* may be responsible.

ANE is often associated with significant morbidity. Although clinical usefulness of the immunomodulating therapy has not been confirmed, early IVIG and steroid pulse therapy is thought to be associated with better outcomes [3,4].

Antimicrobial therapy for *M. pneumoniae* is more controversial. The resistance against macrolides has increased from 51.1% in the 2011 epidemic to 87.2% in 2015 [5]. Unless the patient responds to macrolides, second line antibiotics should be considered.

Our patient at last follow-up showed only a slight limitation in fine motor movement on the left. He underwent rehabilitation therapy, lasting up to 4 hours per day, for 7 months. Whether his improvement was due to the early immunomodulating therapy or the rehabilitation program is not clear, but rehabilitation should be strongly encouraged.

In summary, we describe a patient infected with *M. pneumoniae* who underwent a fulminant clinical course requiring intubation and intensive care unit care. In general, *M. pneumoniae* infection is benign, but CNS involvement is not so rare, and in some cases can lead to severe ANE. Despite the early detection with brain MRI and administration of immunomodulating therapy and antibiotics, the patient manifested severe neurocognitive impairment. Early immunomodulating therapy is thought to be beneficial, with some but not strong evidence. Fortunately, intensive rehabilitation is highly effective in children. Therefore, in combination with immunomodulating therapy, we strongly recommend an intensive rehabilitation program for patients with neurocognitive sequelae.

This study was approved by the Institutional Review Board of Korea University Anam Hospital (approval number: 2020AN0471). Written informed consent by the patients was waived due to a retrospective nature of our study.

**Conflicts of interest**

Baik-Lin Eun is an editorial board member of the journal, but he was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Conceptualization: BLE and JHB. Data curation: SHP, SO, and JHB. Formal analysis: SO and JHB. Funding acquisition: BLE and JHB. Methodology: BLE and JHB. Project administration: SHP and JHB. Visualization: BLE and JHB. Writing-original draft: SHP. Writing-review & editing: SHP, BLE, and JHB.

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**References**

The congenital myasthenic syndrome (CMS) is a heterogeneous group of disorders of the neuromuscular junction [1]. Suspecting and performing a molecular genetic testing is important in CMS considering that the symptoms in this group of disorders are similar, but treatments vary. The syndrome can be classified as presynaptic, synaptic basal lamina associated, and postsynaptic according to the location of the defects and genetic diagnosis [2]. Administration of acetylcholinesterase (AChE) is often the treatment of choice, but caution is required because AChE can aggravate the symptoms in collagen like tail subunit of asymmetric acetylcholinesterase (COLQ)-related CMS (Table 1) [3-5]. Here, we report a first Korean female patient who was diagnosed with COLQ-related CMS with muscle disease gene panel.

A 2-year-old girl was transferred to the pediatric intensive care unit (PICU) of our hospital due to respiratory failure. This was her seventh admission to the PICU due to respiratory difficulty. At the age of 10 days, she developed paroxysmal cyanosis, poor oral intake, and decreased activity and was admitted to the other hospital for the first time due to respiratory failure without pathogen. At the age of 2, 4, 6, and 8 months, she was readmitted due to respiratory failure without pathogen. Only at the age of 11 months, she was admitted to the PICU due to respiratory syncytial virus infection.

On admission, she looked dysmorphic with myopathic face, high arched palate, midfacial hypoplasia and micrognathia. On physical examination, she had low body weight (5.6 kg, < 3rd percentile), normal height (70 cm, 77th percentile), and normal head circumference (41.5 cm, 24th percentile). Physical examination also showed shallow breathing, neck flexor weakness, and generalized proximal dominant motor weakness in both upper and lower extremity, though there were no scoliosis, apparent muscle atrophy, and contractures. However, on neurologic examination, she had a normal deep tendon reflex, and Babinski reflex was not observed.

Her development was delayed. She could sit without aid and crawl, but she could not independently walk at the age of 2 years and spoon.
herself. She was able to make eye contact, smile socially, understand simple instructions, and point out what she wanted. However, she could speak only in monosyllables. Overall, at the age of 2 years, the patient’s motor development was equivalent to approximately 10 months, although her cognitive and language abilities were relatively intact, at approximately 15 months.

Laboratory test results showed carbon dioxide retention on arterial gas analysis (68 mm Hg [normal range, 35 to 45]) and increased ammonia level (155 μg/dL [normal range, 12 to 66]). Except these, laboratory test showed normal complete blood count and normal chemistry test including creatine kinase level and 315Ter and p.Arg236Ter). Chest computed tomography, laryngoscopy, cardiac echocardiography, and cardiac magnetic resonance imaging (MRI) revealed no abnormalities, except a small atrial septal defect. Genetic tests for myotonic dystrophy, spinal muscular atrophy, Prader-Willi syndrome, and Williams syndrome were performed, and all reports were negative. The patient’s beta-glucocebroside level was assessed, and a metabolic workup was subsequently performed, including plasma amino acid, urine amino acid, serum lactic acid, and pyruvic acid. All test results were within the normal ranges, except those of serum lactic acid (3.22 mmol/L [normal range, 0.5 to 2.2]) and pyruvic acid (0.167 mmol/L [normal range, 0.034 to 0.102]). Electroencephalography and brain MRI were performed; however, no abnormalities were identified. She was subsequently referred to another hospital around her home for a follow-up.

At the age of 4 years, the patient was readmitted to our PICU due to respiratory failure. She showed delayed development, muscle weakness with no diurnal variation, and failure to thrive as well as mild ptosis with no diurnal variation and scoliosis with a Cobb angle of 51.0 degrees at T5–T9, which were not observed at the age of 2 years. We performed electromyography and nerve conduction velocity tests. Significant decremental response was observed in the 3-Hz repetitive nerve stimulation test. Subsequently, next-generation sequencing of neuromuscular disease was performed, and the patient was diagnosed with COLQ-related CMS (compound heterozygous mutation in the COLQ gene, p.Arg315Ter and p.Arg236Ter) (Table 2).

After diagnosis, we began treatment with a salbutamol nebulizer (2.5 mg, twice per day) due to the absence of oral salbutamol and have maintained it for 2 years. Subsequently, her motor skills improved significantly. Her myasthenia gravis score improved from 7/39 (1 month after salbutamol treatment) to 14/39 (14 months after salbutamol treatment). In the 6-minute walking test performed, her walking distance was 130 m, and she was able to walk for 5 minutes (4 months after salbutamol treatment). We rechecked the same test at 14 months after salbutamol treatment; her walking distance was 135 m, and she could walk for 6 minutes. In particular, after beginning salbutamol treatment, she has not been admitted to our hospital and has not shown relapse or need for hospitalization in the PICU. Encouraged by these results, we increased the number of salbutamol treatments from two to four per day, and there have been no side effects so far.

To the best of our knowledge, this was the first reported case of the rare CMS in the Republic of Korea. When physicians encounter a patient with recurrent respiratory failure, they investigate the cause of the symptoms in the cardiovascular, pulmonary, and cen-

#### Table 1. Summary of results of a few previous COLQ-mutant congenital myasthenic syndrome studies

<table>
<thead>
<tr>
<th>Publication year</th>
<th>Country</th>
<th>No. of patients with COLQ</th>
<th>Mean age of onset/mean diagnostic age</th>
<th>Drugs received anytime during the whole course of illness (dose)</th>
<th>Response to drugs (I/NR/W–)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>Turkey</td>
<td>4</td>
<td>At birth/6.6 yr</td>
<td>Pyridostigmine (orally 2 mg/kg/day in patient no. 3)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3,4-diaminopyridine (orally 15 to 40 mg/day in patient nos. 1, 3, and 4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oral salbutamol (0.1 mg/kg/day in patient no. 2), intravenous ephedrine (0.5–1 mg/kg/day in patient nos. 1 and 4), extended-release oral albuterol (16 mg/day in patient no. 3)</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>France</td>
<td>15</td>
<td>23.5 mo/23 yr</td>
<td>3,4-diaminopyridine (30 to 60 mg/day in 8 patients), pyridostigmine (in 11 patients), ephedrine (in 3 patients)</td>
<td>NR/W</td>
</tr>
<tr>
<td>2015</td>
<td>Canada</td>
<td>2</td>
<td>At birth/no data</td>
<td>Pyridostigmine, 3,4-diaminopyridine</td>
<td>NR/I</td>
</tr>
<tr>
<td>2019</td>
<td>Turkey</td>
<td>5</td>
<td>8.7 mo/5.2 yr</td>
<td>Ephedrine (0.5–1 mg/kg/day), salbutamol (0.1 mg/kg/day)</td>
<td></td>
</tr>
<tr>
<td>2019</td>
<td>India</td>
<td>4</td>
<td>7.3 yr/13 yr</td>
<td>Salbutamol (5–10 mg/day), neostigmine (30–60 mg/day in one patient)</td>
<td></td>
</tr>
</tbody>
</table>

COLQ, collagen-like tail subunit of asymmetric acetylcholinesterase; I, improved; NR, no response; W, worsened; P, pyridostigmine; N, neostigmine; E, ephedrine; D, 3,4-diaminopyridine; S, salbutamol; A, albuterol.
tral nervous systems. However, as in our case, there may be other causes of recurrent respiratory failure. Because accurate diagnosis and appropriate evidence-based treatment can improve the quality of life in patients with CMS, we recommend that healthcare providers, specifically PICU physicians, consider recurrent respiratory failure as one of the clinical presentations of CMS and that they perform the relevant genetic evaluation. If COLQ-mutant CMS is confirmed, physicians should try to treat the patients using a salbutamol nebulizer.

This study was approved by the Yonsei University College of Medicine Institutional Review Board and the Research Ethics Committee of Severance Hospital (study approval number: 2019-3673-002). Written informed consent by the patients was waived due to a retrospective nature of our study.

### Conflicts of interest

Hoon-Chul Kang is an associate editor, Se Hee Kim is an editorial board member of the journal, but They was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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### Author contribution

Conceptualization: HGK and SHK. Data curation: HGK. Visualization: HGK and SHK. Writing-original draft: HGK. Writing-review & editing: HGK, JSL, KWK, HCK, and SHK.

### References


### Table 2. Genetic and demographic characteristics of patient in our case

<table>
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<th>Characteristic</th>
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<td>Age/age at presentation to the clinic (mo)</td>
<td>71/24</td>
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<tr>
<td>Age at diagnosis/follow-up time (mo)</td>
<td>50/47</td>
</tr>
<tr>
<td>Family history/consanguinity</td>
<td>–/–</td>
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<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td>Korea</td>
</tr>
<tr>
<td>Delayed motor milestones/jump/walk upstairs or downstairs in adult manner/3-word sentences/count 1 to 10 (at the age of 5 years)</td>
<td>+/-/+-/+-</td>
</tr>
<tr>
<td>Facial deformity/ptosis/ophthalmoparesis/facial weakness/dysphagia</td>
<td>+/-/+-/+-</td>
</tr>
<tr>
<td>Respiratory crises</td>
<td>+</td>
</tr>
<tr>
<td>Slow pupillary light response/proximal weakness/distal muscle weakness/neck muscles weakness/scoliosis or kyphosis</td>
<td>ND/+/+/+/+</td>
</tr>
<tr>
<td>Electrophysiological studies</td>
<td></td>
</tr>
<tr>
<td>RNS decrement before salbutamol/after salbutamol treatment</td>
<td>+/-</td>
</tr>
<tr>
<td>Double CMAP</td>
<td>–</td>
</tr>
<tr>
<td>Negative response to acetylcholinesterase inhibitors</td>
<td>+</td>
</tr>
<tr>
<td>Mutations</td>
<td>COLQ, p.Arg315Ter and p.Arg236Ter</td>
</tr>
<tr>
<td>Treatment (dose)</td>
<td>Salbutamol nebulizer (2.5 mg twice up to 4 times per day)</td>
</tr>
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</table>

+, yes; –, no; ND, no data; RNS, repetitive nerve stimulation; CMAP, compound muscle action potential; COLQ, collagen like tail subunit of asymmetric acetylcholinesterase.
Postictal hypoperfusion and hypoxia have been the proposed mechanisms of postictal behavioral dysfunctions such as postictal paresis, amnesia, and confusion [1,2]. Postictal perfusion changes can be detected using various arterial spin labeling (ASL) magnetic resonance imaging (MRI) techniques used to evaluate cerebral blood flow by magnetically labeled arterial blood [3]. Experimental animal studies suggest that postictal hypoperfusion may be mediated by arteriole vasoconstriction [1]. However, the evidence of accompanying vascular changes supporting this theory in humans is insufficient. In the present letter, we report a patient who presented with reversible hemispheric hypoperfusion on three-dimensional pseudo-continuous arterial spin labeling (3D-pCASL) with reversible vascular changes after a prolonged seizure, which may be the underlying pathogenic mechanism of postictal hypoperfusion.

A 7-year-old girl presented to the emergency room due to a seizure that lasted for 30 minutes. She had a generalized tonic seizure which stopped after administering intravenous (IV) lorazepam and IV fosphenytoin within 10 minutes of arrival. The initially focal onset or lateralized sign was unclear. The total seizure duration was approximately 40 minutes. After the seizure termination, she was drowsy and ataxic. She had no fever, and no signs of meningeal irritation were observed. Her vital signs were as follows: body temperature 36.0°C, pulse rate 132 beats/min, respiratory rate 24 cycles/min, and blood pressure 100/60 mm Hg.

Written informed consent by the patients was waived due to a retrospective nature of our study. She was born full term, and perinatal and developmental histories were unremarkable. This was her second seizure, her first one being an unprovoked seizure 9 months prior. Otherwise, she was healthy before admission. At arrival, venous blood gas analysis revealed respiratory acidosis (pH 7.16, pO₂ 56.3 mm Hg, pCO₂ 84.6 mm Hg, HCO₃⁻ 30.1 mmol/L, and SaO₂ 77.8 %), which resolved soon after treatment. Results of other blood tests were as follows: white blood cell counts, 12,600/μL; hemoglobin, 12.0 g/dL; platelet, 582 K/μL; sodium, 139 mEq/L; potassium, 3.9 mEq/L; calcium, 9.5 mg/dL; glucose, 145 mg/dL; magnesium, 0.71 mmol/L; alanine aminotransferase, 8 IU/L; aspartate aminotransferase, 30 IU/L; creatine kinase, 153 U/L; lactate, 0.8 mmol/L; and ammonia, 73 μmol/L. Other laboratory findings were unremarkable.
The patient’s first MRI—which aimed to detect acute brain injuries causing the prolonged seizure—comprised 3D-pCASL, diffusion-weighted imaging (DWI), and phase contrast magnetic resonance angiography (PC MRA), performed 80 minutes after the seizure termination (Fig. 1A). The patient was sedated, but not hemiplegic. DWI revealed no visible diffusion-restricted lesion. However, 3D-pCASL revealed hypoperfusion in the right hemisphere (RH). The left hemisphere (LH) seemed relatively hyperperfused (Fig. 1A, left). Cerebral vascularity on PC MRA also decreased in the RH (Fig. 1A, right). A full sequence MRI including 3D-pCASL and time-of-flight (TOF) MRA was performed 4 hours after seizure termination (Fig. 1B). 3D-pCASL revealed slightly improved but residual hypoperfusion in the RH and reduced hyperperfusion in the LH, suggesting a recovery phase (Fig. 1B, left). Vascular changes were not observed in TOF MRA (Fig. 1B, right). A third MRI, including 3D-pCASL and both PC MRA and TOF MRA, was performed 26 hours after the seizure termination (Fig. 1C). The asymmetric perfusion changes had disappeared (Fig. 1C, left). Subtle decreased vascularity in the RH was suspected in PC MRA but not in TOF MRA (Fig. 1C, middle and right). Electroencephalogram (EEG) on the second day of admission revealed occasional spike or polyspike and wave complexes in the right parieto-occipital and right temporal areas (Fig. 2).

After admission, the patient was alert and did not present further

---

**Fig. 1.** Serial magnetic resonance imaging (MRI) with three-dimensional pseudo-continuous arterial spin labeling (3D-pCASL) and arteriographies of the patient. Mean cerebral blood flow (CBF). Mean CBF was calculated from 10 regions of interest (ROIs) of both the right hemisphere (RH) and left hemisphere (LH) (right and left prefrontal, frontal, temporal, parietal, periventricular areas, total area of ROIs: RH 14,838 mm², LH 14,843 mm²). The first MRI was performed 80 minutes after seizure. 3D-pCASL revealed hemispheric hypoperfusion on the RH and relative hyperperfusion in the LH (mean CBF: RH 41.4 cm/sec, LH 81.9 cm/sec) (A, left). Phase contrast magnetic resonance angiography (PC MRA) revealed decreased cerebral vascularity on the same side (arrows) (A, right). The second MRI was performed 4 hours after seizure termination. 3D-pCASL revealed slightly improved, but remaining hypoperfusion in the RH and decreased hyperperfusion in the LH (mean CBF: RH 44.1 cm/sec, LH 65.6 cm/sec) (B, left). The vascular change was not visible on time-of-flight (TOF) MRA (B, right). The third MRI was performed 26 hours after seizure termination, and asymmetric perfusion changes had disappeared (mCBF: RH 50.8 cm/sec, LH 50.6 cm/sec) (C, left). Subtle decreased vascularity was observed in PC MRA, but vascularity in TOF MRA was normal (triangle) (C, middle and right).
seizures. However, she developed mild fever (37.8°C) and respiratory symptoms; she received IV antibiotics and IV levetiracetam (10 mg/kg/day). On the second day of hospitalization, she was ataxic and presented severe headache, aggression, and irritability. Considering the possibility of levetiracetam-induced personality change, the anticonvulsant was changed to IV valproate (10 mg/kg/day). However, her behavioral changes lasted for another 2 to 3 days. Nasopharyngeal swab test for respiratory virus polymerase chain reaction identified parainfluenza virus. She gradually recovered by the fifth day of hospitalization and was discharged with a prescription of valproic acid. She had no residual neurologic deficit at discharge.

ASL is a safe, easy, non-contrast imaging study for tracking perfusion changes. Previous studies with ASL showed that postictal hypo-/hyperperfusion changes were co-localized to the seizure onset zone (SOZ) in 60% to 100% of patients [2]. However, the timing of ASL acquisition during the postictal period may be crucial in detecting perfusion changes. Most human studies were conducted during the interictal period with various acquisition timings.

In animal studies, postictal hypoperfusion was observed at the SOZ for up to 60 minutes [4]. In the recent prospective study of Gaxiola-Valdez et al. [2], ASLs were performed within 90 minutes after a habitual seizure, and hypoperfusion was observed in 71.4% of the patients. Moreover, the location of hypoperfusion was in accordance with the presumed SOZ in 80% of patients [2]. In the present case, spike discharges from right parieto-occipital region were seen in the interictal EEG on the second day of hospitalization. Based on the results from Gaxiola-Valdez et al. [2], these areas are likely to relate to SOZ. However, the mild voltage attenuation in the left fronto-temporal area was not relevant to the findings on a concurrently conducted ASL.

The current study demonstrated postictal hypoperfusion in the hemisphere including SOZ with contralateral hyperperfusion and serial disappearance. Concomitant vascular changes were observed in PC MRA, which detected relatively slow blood flow. Thus, the decreased vascularity in PC MRA might be associated with vasoconstriction of smaller arteries, as compared to that of larger arteries observed in TOF MRA. The patient’s prolonged behavioral changes might be attributed to the severe hemispheric hypoperfusion. Although levetiracetam may have caused the behavioral changes as an adverse effect, these changes persisted for a few days after stopping levetiracetam. The limitation of this study was that both PC MRA and TOF MRA could not be performed during the first MRI due to an emergency setting. Although it is not always feasible to perform an ASL MRI in emergency situations, it takes less time than a full sequence MRI. Performing ASL will provide more information on seizure-related changes. Additionally, concomitant PC MRA may suggest the underlying reversible vascular changes.

This study was approved by the Institutional Review Board of Hanyang University Guri Hospital (2020-11-009). Written in-
formed 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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**Author contribution**

Conceptualization: HLY, YJC, JHM, HJJ, and DWP. Data curation: HLY, YJC, JHM, HJJ, and DWP. Formal analysis: HLY, YJC, JHM, HJJ, and DWP. Methodology: HLY, YJC, and JHM. Project administration: HLY, YJC, and JHM. Visualization: HLY and JHM. Writing-original draft: HLY and JHM. Writing-review & editing: HLY, YJC, and JHM.

**References**


2. Gaxiola-Valdez I, Singh S, Perera T, Sandy S, Li E, Federico P. Seizure onset zone localization using postictal hypoperfusion detected by arterial spin labelling MRI. Brain 2017;140:2895-911.


Instructions to authors

Enacted: January 31, 2019

General information

*Annals of Child Neurology* is an official publication of the Korean Child Neurology Society. Its formal abbreviated title is "Ann Child Neurol". It is a peer-reviewed open access journal of medicine published in English. The journal was launched in September 30th, 1993 under the title of 'Journal of the Korean Child Neurology Society' until December 31st, 2018 (pISSN 1226-6884). Since 2019, the title is now changed to 'Annals of Child Neurology'. The Journal is published four times per year on the last day of January, April, July, and October. Anyone who would like to submit a manuscript is advised to carefully read the aims and scope section of this journal. Manuscripts submitted to Annals of Child Neurology should be prepared according to the following instructions. For issues not addressed in these instructions, the author is referred to the International Committee of Medical Journal Editors (ICMJE) "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (http://www.icmje.org/recommendations/).

Aims and scope

*Annals of Child Neurology* is an interdisciplinary peer-reviewed biomedical journal publishing articles in the fields of child neurology, pediatric neurosurgery, pediatric neuroradiology, child psychiatry, pediatric neuropsychology, developmental and behavior pediatrics, pediatric 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.

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

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The Journal adheres to the guidelines and best practices published by professional organizations, including Recommendations from ICMJE and Principles of Transparency and Best Practice in Scholarly Publishing (joint statement by COPE, DOAJ, WAME, and OASPA; http://doaj.org/bestpractice/).

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