Aims and scope

Annals of Child Neurology is an interdisciplinary peer-reviewed biomedical journal publishing articles in the fields of child neurology, pediatric neuropsychology, 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, neuroimaging, neuromuscular medicine, neuroimmunology and inflammation, neuro-oncology, deep 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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Focal cortical dysplasia (FCD) is the most common cause of intractable focal epilepsy in children undergoing epilepsy surgery. In these patients, seizures usually develop in early childhood and are often explosive from their onset. This review summarizes the classification of FCD and provides recent updates, clinical features, and illustrative electrophysiological and neuroimaging findings, which are expected to help physicians better understand FCD. Children with intractable focal epilepsy should receive timely evaluations for epilepsy surgery. Complete resection of the epileptogenic zone and an early surgical intervention lead to favorable surgical outcomes.

**Keywords:** Malformations of cortical development; Pediatrics; Epilepsy

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**Introduction**

Focal cortical dysplasia (FCD) is a subgroup of malformations of cortical development characterized by abnormal cortical laminatation, neuronal migration, and differentiation. The neuropathological features were first described by Taylor et al. [1] in 1971 in the pathological specimens of ten patients with drug-resistant epilepsy. FCD is the most common etiology in children with intractable focal epilepsies requiring resective epilepsy surgery, whereas hippocampal sclerosis is the most common cause in adults [2].

Magnetic resonance imaging (MRI) technology has evolved markedly in the last few decades and enhanced the diagnostic yield for FCD. However, delineating the extent of dysplastic lesion in patients with subtle MRI findings, and identifying the extent of the epileptogenic zone (EZ) remains a challenging task. Electrophysiology and functional imaging techniques are helpful in the localization of the EZ.

In this article, we review classification of FCD with recent updates, clinical features, and illustrative electrophysiological and neuroimaging to help the physician understand FCD and provide the best therapeutic options for children with FCD.

**FCD Types and Classification**

Historically, several classification systems for FCD have been proposed [3,4]. In 2011, the International League Against Epilepsy (ILAE) Task Force suggested a three-tiered FCD classification based on histopathological features (Table 1) [5]. This system differentiates isolated FCDs (FCD type I and II) from variants associated with potentially epileptogenic lesions (FCD type III). FCD type I is characterized by isolated dyslamination without any cyto-logic abnormality. Radial dyslamination (FCD type Ia) is characterized by radial microcolumns composed of more than eight neurons aligned in a vertical direction. Tangential dyslamination (FCD type Ib) refers to the derangements of the six layered horizontal composition of the neocortex. The FCD type Ic is a combination...
**Table 1. ILAE classification of focal cortical dysplasia and suggestions for an updates**

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ILAE, International League Against Epilepsy; FCD, focal cortical dysplasia; mTOR, mammalian target of rapamycin.

of both radial and tangential variants. FCD type II refers to disruptions of cortical lamination with dysmorphic neurons. Dysmorphic neurons are the histopathological hallmark of FCD type II lesions. They have enlarged cell body and nucleus with aggregates of Nissl substance and accumulation of neurofilament proteins. Balloon cells, observed exclusively in FCD type IIb, present enlarged cell body and opalescent glassy eosinophilic cytoplasm in hematoxylin-eosin stain. FCD type III refers to cortical lamination abnormalities (FCD type I) associated with or adjacent to other principal lesions. Principal lesions comprise any anatomical lesion with etiologically defined pathogenesis, including epilepsy-associated tumors, vascular malformations, encephalitis, traumatic scars, malformations of cortical development, or mitochondrial/metabolic dysfunction. Dual pathology refers only to patients with hippocampal sclerosis, who have a second epileptogenic principal lesion. Of note, cortical dyslamination in the temporal lobe associated with hippocampal sclerosis is considered as FCD type IIIa, rather than dual pathology. Double pathology refers to two independent epileptogenic lesions, which evolve from independent pathogenesis, not including hippocampal sclerosis. The current ILAE classification presents several challenges. Najm et al. [6] have published a proposal to revise and update the 2011 ILAE classification (Table 1). First, there are concerns about the limited clinical and radiological significance in FCD Ib and Ic. Molecular biomarkers to differentiate FCD Ib and Ic need to be introduced. Second, there is increasing evidence for the role of somatic mammalian target of rapamycin (mTOR) pathway activation in the pathophysiology of FCD type II [7-9]. This would differentiate type II patients with mTORopathies, who could be potential candidates for mTOR inhibitors. Although mTORopathies are associated with 10% to 20% of FCD type II lesions, Najm et al. [6] suggested that molecular genetic findings of mTOR activation using pathogenic tissue need to be classified as a separate entity in FCD type II. Moreover, new variants of the bottom-of-sulcus type II need to be distinguished. Bottom-of-sulcus dysplasias (BOSDs) are highly epileptogenic clinicoradiologic-histopathologic entities with continuous, localized, rhythmic interictal epileptiform discharges [10]. The characteristic MRI features of BOSDs include cortical thickening, gray-white blurring, increased subcortical T2, fluid attenuation inversion recovery (FLAIR), and a transmantle sign [11]. MRI lesions of BOSDs are highly co-registered with hypometabolism on 2-deoxy-2(18F) fluoro-d-glucose positron emission tomography (FDG-PET) [12]. BOSDs are characterized by neuronal dyslamination and dysmorphism at the sulcal depth and a relatively normal gyral crown [13]. The surgical outcome of seizure freedom is as high as 90% if BOSDs are completely resected [10]. Najm et al. [6] have suggested that molecular and genetic mechanisms are needed for a comprehensive classification based on clinical features, imaging characteristics, histopathological findings, and treatment options to classify patients in clinical setting.

**Clinical Features**

Epilepsy is the most common clinical presentation for FCD. Seizures may start at any age, but usually, develop in early childhood. FCD with cytoarchitectural abnormalities (FCD type IIa and IIb) is associated with earlier age of seizure onset than FCD with architectural abnormalities alone (FCD type Ia) [14,15]. The seizure...
frequency is usually high, and seizure onset is often explosive, needing occasional hospitalization. In a cohort of 32 patients with FCD type IIb who ultimately underwent resective surgery, 23 patients (72%) had multiple daily seizures [10].

Most children with FCD present with focal seizures depending on the location of the lesion. However, in very young children, seizure can be generalized, generalized electroencephalography (EEG) abnormalities, and epileptic encephalopathy. Fauser et al. [14] described generalized tonic-clonic seizures in 20.6% of patients, tonic seizures in 15.9% of patients, and atonic seizure in 6.5% of patients. Epileptic spasms, often asymmetric or asynchronous, can be the first seizure type in infants [16].

Seizures are usually pharmacoresistant and may require epilepsy surgery. In contemporary surgical series, cortical dysplasia is the most common pathological substrate in children undergoing epilepsy surgery [17]. However, a minority of patients have shown transient response to medication and remained seizure-free for several years [14].

Neurocognitive dysfunction is also problematic in children with FCD. Intellectual disabilities have been demonstrated in approximately 26% to 79% of children with FCD [18, 19]. Krsek et al. [20] observed higher rates of cognitive impairment in FCD type I patients (96%) than in FCD type II patients (27%). Their study showed that 31% to 57% of children exhibited motor or language development delays. Conversely, another study showed that children with FCD type II were more likely to have lower intelligence quotient than those with FCD type Ia [15]. Such inconsistencies may be related to clinical factors such as the age of epilepsy onset, the extent of FCD lesion, and the duration of epilepsy. The pathophysiology of neurocognitive dysfunction in FCD remains unclear. However, the detrimental influences of frequent early seizures on the cognitive potential of children are well-documented [21-23]. Therefore, early surgical intervention in intractable epilepsy should be considered to stabilize cognitive function.

Diagnostic Evaluations

1. Electroencephalography

1) Scalp EEG

Studies have shown that the most characteristic interictal pattern consisted of continuous rhythmic or pseudo-rhythmic spikes or sharp waves, observed in 40% to 64% of cases [12,24]. The interictal EEG could display focal or regional spikes or polyspikes, focal background slowing, spike trains or continuous epileptiform discharges. Interictal EEG findings did not distinguish between patients with mild and severe cortical dysplasia. Moreover, there were no differences in the incidence of localized interictal epileptiform discharges between mild and severe dysplasia [24,25]. Scalp EEG is limited in its spatial resolution and ability to detect activity generated deep in the brain. However, a recent study showed a correlation between scalp and intracranial EEG (iEEG) seizure-onset pattern (SOP). In a comparison of SOP in 61 patients with focal epilepsy, ≥ 13 Hz paroxysmal fast activity on scalp EEG corresponded to low-voltage fast activity (LVFA) at iEEG onset in patients with malformations of cortical development [26].

2) Intracranial EEG

iEEG provides information about the ictal onset zone with a seizure propagation pattern. It can also identify functional areas or eloquent cortex. The main indications for iEEG monitoring are: the FCD is invisible or ill-defined on MRI, a discordance between electro-clinical data and presurgical evaluation, or in case of proximity or involvement of eloquent cortex [27].

Typical interictal iEEG features are rhythmic spike discharges (RSDs) or pseudorhythmic spikes (Fig. 1). A study showed that the intracranial interictal activity was characterized by continuous rhythmic, or pseudorhythmic spikes or polyspikes with a frequency between 1 to 3 Hz [19]. The frequency of RSDs was usually maximized within the location of FCD. However, RSDs can be seen in multiple pathologies with epileptogenicity, not specific for FCD. Interictal RSDs are as important as ictal discharges. The typical interictal pattern has the highest sensitivity for the EZ [28]. The intracranial interictal discharges were modulated by sleep stages, with an increased prevalence of rhythmic discharges in drowsiness and non-rapid eye movement (NREM) sleep and decreased discharges during REM sleep [29].

Ictal discharges frequently arise from the same areas as the RSDs, and their area is often larger than the interictal activity. Five ictal onset patterns have been described in FCD: (1) LVFA; (2) spike-and-wave activity; (3) sharp activity at ≤ 13 Hz; (4) alpha-theta sharp waves; and rarely (5) delta brush [30,31]. Overall, the most common pattern was LVFA [32,33]. LVFA is defined as clearly visible rhythmic activity > 13 Hz, usually with low initial amplitude < 10 to 30 μV (Fig. 2). Spike-and-wave activity indicates medium to high voltage spike-and-wave complexes typically occurring at a frequency of 2 to 4 Hz. Sharp activity at ≤ 13 Hz is identified as low to medium voltage sharply-contoured rhythmic activity, most commonly in the alpha-theta range. Delta brush characterized by rhythmic delta waves at 1 to 2 Hz with superimposed 20 to 30 Hz brief bursts of activity overriding each delta wave are rarely seen. These delta brush pattern has been observed in premature infants and patients with anti-N-methyl-D-aspartate receptor encephalitis [34,35]. Lagarde et al. [36] demonstrated the SOP prevalence, according to the types of FCD. LVFA was the...
most frequently observed, but slow or rhythmic activities were also seen at seizure onset in patients with FCD type I. In FCD type II, preictal spiking or burst of polyspikes followed by LVFA were the most frequent patterns.

High frequency oscillations (HFOs), namely ripples and fast ripples, are reliable biomarkers of epileptogenicity and good indicators of seizure onset zones (SOZ) [37,38]. HFOs, which reflect pathological hypersynchronous events, are usually recorded from implanted intracranial micro-electrodes with sampling rates of 1,000 Hz or higher. They can also be detected with macro elec-

Fig. 1. Continuous rhythmic spike discharges with the frequency of 1.5 to 2 Hz. In this interictal intracranial electroencephalography recording from a patient with right postcentral focal cortical dysplasia type IIb, continuous rhythmic high voltage spike discharges were recorded at contacts Ch 4, 5, 6, 11, and 12. Electrode contacts of Ch 4, 5, 6, 11, and 12 were located in lesional/perilesional tissue.

Fig. 2. Low-voltage fast activity at seizure-onset. In this ictal intracranial electroencephalography recording from a patient with right postcentral focal cortical dysplasia type IIb (the same described in Fig. 1), seizure-onset (arrows) was characterized by a visible rhythmic activity at 20 to 30 Hz, initially <10 uV in amplitude, which remained confined for several seconds to Ch 21, 29, 46, 51, and 52. Electrode contacts of Ch 21, 29, 46, 51, and 52 were considered as seizure-onset zone.
trodes during short-term electrocorticography in the operating room. HFOs are recorded when the EEG is high-pass filtered at 80 and 250 Hz using a finite impulse response filter to eliminate ringing. A ripple is defined if an event is visible between 80 and 250 Hz, whereas a fast ripple is defined an event visible on the side of the 250 Hz filter. Spikes and HFOs are generated as a result of hypersynchronous events and may co-occur frequently. A study revealed the rates and durations of HFOs were frequent and longer in the SOZ than outside of the SOZ [39]. Although HFOs could occur independently of spikes, spikes with fast ripples determined SOZ with the highest sensitivity [37,40]. As the rates of HFOs are high in FCD, they can be reliable biomarkers to define the extent of the epileptogenic dysplastic tissue in FCD [41]. Additionally, HFO rates differ across lesional, perilesional, and nonlesional tissue in FCD, being higher within the borders of the MRI-visible dysplastic lesion and rare in the remote cortex [42]. Although it is difficult to differentiate between pathologic and physiologic HFOs, resection of brain tissue generating high rates of HFOs in addition to the SOZ would lead to better seizure outcomes [40,43]. Seizure propagation from SOZ can also display typical SOPs, such as sharp activity at 13 Hz and LVFA [31]. A study showed the rapid propagation from SOZ in patients with FCD than in those with nondysplastic lesions [44].

2. Magnetic resonance imaging
There are several characteristic features on MRI that identify the dysplastic cortex. MRI findings include: (1) increased cortical thickness, often associated with abnormal gyral patterns; (2) blurring of gray-white matter junction on T1-weighted images and T2-weighted images; and (3) increased T2 and FLAIR signal intensity in subcortical white matter and cortical gray matter (Fig. 3). Abnormal cortical gyrations and sulcations are better evaluated by three-dimensional (3D)-volume sequences and surface rendering reconstructions. The transmantle sign is a T2-weighted white mat-
ter signal hyperintensity tapering toward the ventricle [13]. It is reported to be specific to FCD type II but is found in only 34% of the FCD type II patients.

Studies have reported normal MRI findings in 20% to 50% of patients with FCD [24,45]. MRI features are often subtle and difficult to detect, especially in FCD type I. Even with experienced neuroradiologists, 40% of patients with FCD type I and 10% to 20% of patients with FCD type II are reported to be MRI-negative [46,47]. In infants with an incompletely myelinated brain, abnormalities in signal intensity of white matter with blurred gray-white matter can be seen as a normal finding. Thus, FCD lesions in infants could become less distinct or disappear with the maturation of myelination. Conversely, the lesions could become evident over time as myelination progress from 41% to 88% [48]. Therefore, interpreting the brain MRI of infants requires caution in differentiating between true dysplasia and the process of myelination.

Advances in MRI techniques and additional sequences can be helpful in the detection and delineation of the dysplastic lesion [49,50]. Morphometric MRI analysis is a voxel-based imaging processing method that identifies differences in brain anatomy with groups and compares them with a standard database [51]. Diagnostic yield of dysplastic lesion is improved by morphometric MRI combined with conventional visual analysis [52]. Higher magnetic field MRI has immense potential to identify and characterize otherwise inconspicuous lesions accurately [53,54]. Over the last several years, ultra-high-field (UHF) 7T MRI has been available in research settings and has shown exceptional diagnostic benefits [55,56]. Owing to a higher signal-to-noise ratio and smaller voxel size for a given acquisition time, UHF MRI allows for better depiction and visualization of FCD [57,58]. Several high-resolution structural sequences have been introduced and considered a promising approach for the improvement of FCD diagnosis. Magnetization prepared 2 rapid acquisition gradient echoes (MP2RAGE) is a 3D T1-weighted sequence with a sharp contrast between gray and white matter and minimal effect of B1 inhomogeneity [59]. This MP2RAGE can be a suitable sequence to delineate the lesion with high gray-white matter contrast, such as FCD [60]. A new sequence called fluid and white matter suppression (FLAWS) has been reported to be useful for the detection of FCD EZs [61]. FLAWS sequence acquires two images of 3D high spatial resolution images with white-matter signal suppression and cerebrospinal fluid (CSF) signal suppression. Following FLAWS-contrast images are calculated by suppressing both the white matter and CSF signals, which results in high gray-matter specific contrast.

Ultra-high resolution and new sequences would provide opportunities for a successful surgical option to patients with MRI-negative intractable focal epilepsy. Although detection rates have been increased, delineating the extent of the epileptogenic lesion on the

Fig. 4. Features of neuroimaging in a 6-year-old girl with left parieto-temporal focal cortical dysplasia type IIb. (A) Interictal 2-deoxy-2(18)F fluoro-d-glucose positron emission tomography shows hypometabolism in the left parieto-temporo-occipital area. (B) Ictal single-photon emission computed tomography demonstrates hyperperfusion in the left parieto-temporal area.
structural MRI still needs to be solved. For surgical resection planning, multimodality presurgical evaluation and MRI analysis play an essential role in determining the localization and extent of EZ.

3. Positron emission tomography
PET is a nuclear medicine imaging modality based on the metabolism of FDG. FDG is a glucose analog that can be transported into the cell by the glucose transporter 1 (GLUT1) receptor. FDG does not undergo glycolysis process and becomes metabolically trapped within the cell, serving as a marker for tissues with higher metabolism. As the half-life of FDG is extremely short, it is often difficult to obtain reliable ictal PET. Therefore, the majority of patients are scanned in the interictal phase with hypometabolism in EZ (Fig. 4A). Interictal hypometabolism of FDG-PET can localize FCD in approximately 75% to 83% of patients [24,62]. FDG-PET is highly informative in patients with MRI-negative epilepsy [12,63]. In a series of 23 patients with negative MRI with histologically proven Taylor-type FCD, FDG-PET showed high sensitivity (78%) for detecting FCD [63]. In their study, identification of Taylor-type FCD was increased up to 95% with MRI coregistration. FDG-PET/MRI coregistration improved the detection of FCD and proved useful for planning iEEG studies in patients with normal MRI [64].

4. Single-photon emission computed tomography
Single-photon emission computed tomography (SPECT) is a nuclear medicine imaging modality that allows the quantitative and qualitative assessment of regional cerebral blood flow. SPECT requires an intravenous injection of a radioactive tracer to monitor cerebral blood flow. There is increased ictal regional cerebral blood flow or decreased uptakes in the inter-ictal phase (Fig. 4B). Subtraction ictal SPECT co-registered MRI (SISCOM) utilizes subtraction of interictal SPECT from the ictal SPECT and the resulting image is co-registered with MRI. SISCOM has helped to localize epileptogenic foci in presurgical evaluation, especially in patients with intractable epilepsy [65,66]. Studies indicate that the sensitivity of SPECT for detecting FCD is 87% to 89% [67,68]. The injection time is critical for ictal SPECT. A study showed that an injection time less than 30 seconds corresponded to a well-localized SPECT image [69]. Early radiotracer injection is important for successful seizure localization with ictal SPECT. Performing ictal SPECT in pediatric patients may be complicated as it may be difficult to recognize the clinical onset of seizures and rapid propagation of seizure activity. However, ictal SPECT provides additional relevant data to localize the EZ in children with FCD [70]. Moreover, it has a predictive value for favorable surgical outcomes when the zone of ictal SPECT hyperperfusion is completely resected [69,71].

Surgical Outcome
Epilepsy surgery is a safe and effective treatment option in children with drug-resistant epilepsy. The surgical approach depends on the extent of the dysplastic cortex based on the presurgical evaluation. Focal or lobar resection is the most common neurosurgery performed in FCD [17]. Corpus callosotomy, hemispherectomy, and vagus nerve stimulation can be considered as palliative surgery, depending on the patient evaluation.

The overall seizure-free outcome after surgery ranges from 50% to 75% at 2 years after surgery (Table 2) [72-74]. Patients with FCD type IIb have better surgical outcomes than those with mild pathology subtypes [33,45,75]. In a pediatric surgical series by Krsek et al. [20], 75% of FCD type II patients had a favorable outcome, whereas only 21% of FCD type I patients achieved seizure freedom (P < 0.001). In a similar series, 88% of FCD type IIb patients were seizure-free compared with 21% of FCD type I and 57% of FCD type IIa patients [18]. Most seizure recurrences after epilepsy surgery occur during the first 2 postoperative years [18,76,77]. Therefore, postoperative outcomes at 2 years may reflect the long-term seizure outcome. In children who are seizure-free after surgery, withdrawal of antiepileptic drugs (AEDs) is generally considered. AED withdrawal rates after surgery vary from 14% to 48% depending on parental preferences and physician practices [18,78,79]. TimeToStop trial demonstrated that early AED withdrawal did not affect long-term seizure outcome [80]. The European pediatric epileptologists who participated in the TimeToStop study generally started tapering off AEDs between the median of 3 and 5 months after successful epilepsy surgery, which is earlier than nonparticipants [81].

The surgical outcomes vary depending on the patient's age at surgery, pathological substrate, the extent of the lesion, and type of surgery. Studies have reported several prognostic factors associated with favorable surgical outcome in FCD patients (Table 2) [15,18,45,73,82-84]. In a meta-analysis of FCD surgical series, focal seizures, temporal location, detection of MRI lesion, severe type of histopathology, and complete resection were found to be significant prognostic factors [85]. The most important predictor for seizure freedom is complete resection of the EZ [18,45,74,77,83,86,87]. Complete resection of the visible lesion or the EZ was associated with a higher rate of seizure freedom (odds ratio, 3.91; 95% confidence interval, 3.03 to 5.32) [85]. The success of epilepsy surgery depends on the accurate localization and complete resection of the EZ. However, the EZ may not co-localize with the pathology or may be larger than the dysplastic lesion [88]. This issue makes
complete resection of EZ more complex and requires multimodal integrative presurgical evaluation. Studies have shown that MRI abnormalities suggestive of FCD were associated with a higher rate of seizure freedom as compared with a normal MRI scan [18,73,82,83]. However, even in the absence of MRI lesions, it is worthwhile to consider epilepsy surgery in patients with drug-resistant epilepsy [89].

It is widely accepted that early surgical intervention and cessation of seizure activity are crucial for children with intractable epilepsy [90,91]. However, it is not simple to say “the earlier, the better.” In patients with an unclear extent of EZ, or younger age with high perioperative risk, or low sensitivity of MRI, later resections may offer advantages in terms of precision of surgical-resection planning [92]. Early surgical intervention in drug-resistant epilepsy can support functional plasticity in children. However, a complete and precise resection of EZ is of paramount importance.

**Conclusion**

FCD is a significant cause of intractable focal epilepsy and leads to epilepsy surgery in childhood. Epilepsy, neurocognitive dysfunction, and behavioral problems can be present in children with FCD. Integrative evaluations, including electrophysiological studies and neuroimaging, would help to localize and delineate the extent of EZ. Epilepsy surgery can be an effective treatment option for children resistant to medication. Complete surgical resection of EZ based on multimodal evaluations would lead to favorable seizure outcome.

**Conflicts of interest**

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

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Ketogenic diets are high in fat, low in carbohydrates, and contain an adequate amount of protein. In addition to the classic ketogenic diet, three alternative types of ketogenic diet therapies (KDTs) have emerged. In addition to clarifying the indications for early treatment using KDTs, ongoing research over the past decades has led to the recognition of their contraindications and adverse effects. Recent studies focusing on the targeted therapeutic range of KDTs are expected to elucidate the precise mechanisms by which they alleviate certain epilepsy syndromes and other disorders. In this review, we discuss recent advances in KDTs, focusing on six issues: the selection of a specific KDT; the use of KDTs for febrile infection-related epilepsy syndrome and super-refractory status epilepticus; the use of KDTs for infants with refractory epilepsy; links between the gut-brain axis and KDTs; triheptanoin; and the use of KDTs for disorders other than pediatric epilepsy.

**Keywords:** Diet, ketogenic; Drug resistant epilepsy; Child

**Introduction**

Ketogenic diet therapies (KDTs) are the first-line treatment for glucose transporter 1 deficiency syndrome (Glut1DS) and pyruvate dehydrogenase deficiency. KDTs are also an early course of treatment for several epilepsy syndromes, including Dravet syndrome, West syndrome (WS), and epilepsy with myoclonic atonic seizures, and should be offered to children who fail to benefit from two anti-epileptic drugs (AEDs) [1]. Based on clinical experience and research over the last decade, Kossoff et al. [1] updated recommendations for the use of dietary therapies for pediatric epilepsy in 2018 to include new indications, including febrile infection-related epilepsy syndrome (FIRES)/super-refractory status epilepticus (SRSE), Angelman syndrome, complex 1 mitochondrial disorders, and Ohtahara syndrome. The updated recommendations also state that most centers prefer a non-fasting state at initiation of a KDT; making hospital admission optional; that although a diet can be selected from four major KDTs, the classic ketogenic diet (KD) is associated with a higher likelihood of a seizure-free outcome for children under 2 years of age, whereas alternatives to the classic KD are favored for adolescents and adults; and that additional lab tests (e.g., selenium, free and total carnitine) and electroencephalography (EEG) should be performed.

High-fat/low-carbohydrate diets induce production of ketone bodies (KBs), which become the primary source of energy for cell metabolism instead of glucose [2]. KDTs have a broad-spectrum therapeutic range than medications due to their multi-mechanism properties, with KBs directly inhibiting vesicular glutamate trans-
port, altering metabolism by inhibiting glycolysis and increasing mitochondrial adenosine triphosphate (ATP) production, activating ATP-sensitive potassium channels to prevent neuronal excitability, and increasing polyunsaturated fatty acid and decreasing reactive oxygen species by stimulating mitochondrial uncoupling proteins [3,4]. Thus, KDTs not only inhibit neuronal hyperexcitability but also have neuroprotective effects that correct cellular energy failure and guard against epileptic brain damage [3]. Some researchers anticipate that KDTs will be replaced by drugs that mimic the actions of KDTs or directly stimulate ketogenesis in the liver, making these dietary treatments more similar to pharmacological therapy [5-7]. At present, however, this possibility seems questionable because different KDTs involve different subsets of anti-seizure mechanisms that can be targeted to individual patients. In this review, we focus on recent advances in KDTs for pediatric epilepsy considering the following issues: selection of a specific KDT; use of KDTs for status epilepticus; use of KDTs for infants with refractory epilepsy (RE); links between the gut-brain axis and KDTs; triheptanoin; and use of KDTs for disorders other than pediatric epilepsy.

**Selection of a Specific KDT**

As compliance with the strict regimen of the classic KD is difficult, more flexible alternative variants have been employed. In addition to the classic KD, three other major dietary treatments—the modified Atkins diet (MAD), low glycemic index treatment (LGIT), and medium chain triglyceride (MCT) diet—are now available for patients with epilepsy.

The MAD typically consists of a 1:1 to 1.5:1 ketogenic ratio, achieves more than 50% seizure reduction in two-thirds of children with RE [8-11], and is well tolerated by adolescents and adults [12] and those who do not adhere to the classic KD. Some studies report that the MAD is as effective as the classic KD; although, the classic KD is associated with a higher likelihood of seizure freedom in children under 2 years of age with RE [13,14] and epileptic individuals with myoclonic tonic seizures [13]. In addition to its advantages in regard to growth and physical abilities, the MAD can be a good option for long-term maintenance for Glut1DS patients [15]. Nevertheless, for infants with Glut1DS, the classic KD is still considered superior in the early course of treatment and is recommended for long-term maintenance if possible [1].

The LGIT involves swapping high glycemic index (GI) foods for low GI alternatives. The GI describes the tendency of foods to increase blood glucose, compared with an equivalent amount of reference carbohydrate, usually glucose. Thus, the LGIT uses a liberalized but still low carbohydrate intake, with carbohydrates supplied only in the form of low GI foods and allows a more flexible lifestyle for patients by permitting increased intake of carbohydrates [16]. It achieves around 50% seizure reduction in half of pediatric patients with RE [17,18] and is useful for those who cannot tolerate the classic KD or MAD [17]. Considering its high efficacy, the LGIT is used as an alternative or supplementary treatment for Angelman syndrome [19,20].

The MCT diet, which produces MCT (C6-12) that are more ketogenic than long-chain triglycerides, was introduced by Huttenlocher in 1971 [21]. The efficacy of the MCT diet is comparable to that of the classic KD; over half of children achieve more than 50% seizure reduction with good tolerance and few side effects [22,23]. In animal models with MCT diet, KB concentrations in blood plasma are poorly correlated with seizure control [24,25], and there is a lack of evidence that KBs participate in stopping seizures [26]. This suggests that MCTs, rather than KBs, block seizure onset and raise the seizure threshold [27-29]. MCTs, which consist of approximately 60% octanoic acid (C8) and 40% decanoic acid (C10), exert anti-seizure effects via α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) receptor inhibition [26] as well as peroxisome proliferator-activated receptor γ (PPARγ) activation and mitochondrial biosynthesis [29] by using decanoic acid rather than octanoic acid [26,29,30]. In an animal model of acute seizures, decanoic acid increased seizure thresholds in both the 6 Hz stimulation test (a model of drug-resistant seizures) and maximal electroshock test (a model of tonic-clonic seizures), although it did not block pentetrazol-induced seizures (proposed to be a model of absence seizures) [30]. Decanoic acid is considered to be a PPARγ agonist that increases brain mitochondrial function and ATP synthesis, thereby increasing seizure threshold [29,31], but it does not alter glycolytic enzymes [32]. MCTs have the direct and selective action of inhibiting AMPA receptors in an animal model, which has been considered to be the first targeted anti-seizure mechanism of the MCT diet [26]. This gives rise to the question of whether the MCT diet can be replaced by AMPA receptor-blocking agents such as perampanel [33]. However, a recent study showed a synergistic interaction between perampanel and decanoic acid, as perampanel binds at a different AMPA receptor site than decanoic acid [34].

**Use of KDTs for Status Epilepticus**

Although FIRES and SRSE are included in the updated recommendations, the efficacy of KDTs was first shown for refractory status epilepticus (RSE) as described by Kossoff and Nabbout [35] in 2013. At that time, 10 retrospective studies including 32 children and adults with RSE showed dramatic beneficial effects of
KDTs, with 78% of patients becoming seizure-free and most responding within 7 to 10 days. Patients with FIRES are also reported to be good responders to KDTs [36].

Recent studies with 10 or more patients report good outcomes of KDTs regardless of etiology and a low rate of complications in critically ill patients with RSE/SRSE [37-40]. For instance, more than half of patients achieved more than 50% seizure reduction within a median of 7 days, desired ketosis was reached within a median of 4 days, and most patients successfully weaned off continuous infusion of anesthesia within 2 weeks after initiation of a KDT. Relatively low rates of adverse effects were noted, but these included gastrointestinal disturbances, electrolyte imbalance, and ketoacidosis, with the main causes of discontinuation being pancreatitis and hypertriglyceridemia [38,39]. These outcomes are consistent with those of other studies with fewer than 10 patients [41-49], and patients with FIRES have also been found to respond quickly after KDT initiation [40,46,47]. Most patients are good responders, weaning off infusion and successfully reaching ketosis, but the number of AEDs did not change significantly before and after undertaking a KDT [40,43]. The age of patients has varied across studies, but even 6 to 10-week-old neonates with RE are reported to tolerate KDTs well [42,50]. Intravenous (IV) KDT is recommended for patients with underlying concomitant ileus [41,44,48], and early administration of IV KDT should be considered before switching to an enteral route [44]. There are no significant differences in the time to reach ketosis between IV and enteral routes, although hypertriglyceridemia and pancreatitis are frequently associated with IV KDT. Considering that critically ill patients with FIRES/SRSE receive many concurrent medications and are prone to malabsorption, IV KDT could be temporarily substituted for an enteral route [41]. Nonetheless, before evaluating the efficiency and safety of KDTs among FIRES/SRSE patients, factors such as concomitant treatments, variations in timing before the initiation of KDTs, the specific outcomes assessed, and possible publication bias should be considered [38].

Use of KDTs for Infants with RE

Contrary to a conventional view, under 2 years of age may be the optimum time to initiate a KDT because of the metabolic advantages of infants [50-55]. Numerous studies provide evidence for the advantages of using KDTs in infants with RE. Infants under 1.5 years of age have a higher chance of achieving seizure freedom than children over 1.5 years of age, and, interestingly, infants under 9 months of age also have a higher likelihood of achieving seizure freedom, demonstrating the ease of KDT administration and good outcomes before solid feeding [51]. These outcomes remained stable at long-term follow-up. Another study reports specific etiologic differences in long-term seizure-free outcomes among 115 patients who initiated KDTs before 1 year of age and shows that seizure freedom within the first 3 months could be a predictor of long-term seizure freedom [55]. A similar study including 109 patients with RE under 3 years of age with different etiologies reports that patients with a genetic etiology were particularly good responders to KDTs [54], with nearly half of patients with a confirmed genetic abnormality showing more than a 50% reduction in seizure frequency. Nevertheless, most studies report a high efficacy of KDTs for some specific epilepsy syndromes such as WS [53,56-59], epilepsy with myoclonic atonic seizures [14], and Dravet syndrome [60]. Around two-thirds of patients with WS experience a reduction in seizures with KDTs, and many show improvements in development, EEG activity, and number of concurrent AEDs [58]. Adrenocorticotropic hormone (ACTH) treatment is associated with a high responder rate and quick cessation of spasms, but it has higher rates of relapse and adverse effects than KDTs [53]. In a recent study comparing efficacy and safety between KDTs and standard high-dose ACTH treatment in WS infants [59], ACTH was associated with a higher rate of short-term remission among infants without prior treatment history of vigabatrin (VGB); however, it was also associated with a higher rate of relapse and similar rate of seizure-free outcome as KDTs at long-term follow-up. Also, KDTs had a higher rate of seizure freedom in long-term follow-up and a lower relapse rate in the short-term in infants with a prior treatment history of VGB. This study suggests that after VGB failure, a KDT could be a second-line treatment for WS.

The Gut–Brain Axis and KDTs

Several studies show that diversity in the diet significantly influences the composition of gut microbiota and the subsequent health of individuals [61]. Differences in the composition of gut microbiota between drug-sensitive/healthy control individuals and drug-resistant epilepsy patients indicates the possible involvement of dysbiosis in the development of drug-resistant epilepsy [62]. Dysbiosis may enhance susceptibility to seizures and accelerate illness resulting from chronic stress; thus, restoration and remodeling of a healthy gut microfloral population could control seizures and boost quality of life [63,64]. In this regard, KDTs may positively impact seizures via alteration of the gut microbiota. In two mouse models, KDTs altered the composition of gut microbiota, including reducing bacterial alpha diversity and increasing certain bacteria [65]. Moreover, high-dose antibiotics, which deplete gut microbiota, increase seizure vulnerability in wild-type and Kna1–/– mice receiving KDTs. In this study, gut microbiota and KDTs with antiseizure
properties were correlated with decreases in systemic gamma-glutamylated amino acid and enhanced γ-aminobutyric acid (GABA) levels in the hippocampus.

Similar to the results of animal studies, children with RE show alterations in the specific richness and diversity of gut microbiota, such as increased *Bacteroidetes* and decreased *Firmicutes* and *Actinobacteria*, after 6 months of KDT [66]. Moreover, the abundance of *Clostridiales*, *Clostridia*, *Ruminococcaceae*, *Lachnospiraceae*, *Alstipes*, and *Rikenellaceae* were significantly increased in those who failed to respond to KDT compared with good responders. The authors of this study speculated that specific microbiota might be therapeutic targets in the treatment of epilepsy and could serve as biomarkers indicating the efficacy of KDT.

### Triheptanoin

Triheptanoin is a triglyceride composed of three heptanoate (C7 fatty acid) that is an artificial tasteless oil easily dissolved in food. Triheptanoin is used to treat many metabolic disorders because it has an anaplerotic role that replenishes substrates involved in the tricarboxylic acid (TCA) cycle and the ability to bypass metabolic blockade induced by enzyme deficiency [67]. Several studies using acute and chronic seizure mouse models demonstrate that triheptanoin exerts anti-seizure effects by increasing TCA intermediates and activating mitochondrial function, known as anaplerosis [68,69]. Calvert et al. [70] performed a study including 12 children with RE aged 3 to 18 years old and found that (1) children tolerated 30 to 100 mL triheptanoin per day (median, 55.5 mL); (2) the most frequent adverse effect was gastrointestinal disturbance; (3) eight children completed the trial, of whom four safely completed an extended treatment period up to 909 days; (4) five children showed > 50% reduction in seizure frequency, including one patient who was seizure-free for 6 months; (5) children who previously received KDT showed better tolerance and outcomes than those who initiated KDT for the first time, presumably as a result of good parental compliance; and (6) no drug interactions were observed. Therefore, triheptanoin could possibly administered concurrently with AEDs. Another study in adults with RE reported that MCT or triheptanoin treatment was safe, feasible, and well tolerated as an add-on treatment [71]. In this double-blind study including 34 patients who took triheptanoin (n = 17) or MCT oil (n = 17) mixed into food, 11 and nine patients completed the study and showed good tolerance of the treatment at a median dose of 55 and 59 mL for 3 months, respectively, with reported side effects of diarrhea and abdominal pain. Although the aim of this study was not to investigate the efficacy of KDTs, it showed that MCT had good outcomes for focal un-aware seizures. Recent studies examining the use triheptanoin for treating GlutIDS [72-74] show that besides reducing glucose, its main benefit is a reduction in non-paroxysmal events.

### KDTs for Other Neurologic Disorders

KDTs have been used for many neurologic disorders other than pediatric epilepsy, such as adult epilepsy, autism, Alzheimer’s disease, and brain tumors [75]. The use of KDTs for treating autism is increasingly reported and, according to a systematic review in 2015, eight studies (five human and three animal) had tested the effect of KDTs in autism [76]. A prospective pilot study showed that 18 out of 30 children with autism showed better scores on an autism rating scale after KDT [77]. In addition, MCT was described as a potential supplement for mild Alzheimer’s disease [78], and KDTs were proposed as a treatment for Down syndrome [79].

Another current interest is the potential anti-tumor effect of KDTs. Studies suggest that KDTs inhibit tumor cell growth by altering cell metabolism, which seems to enhance the response of other anti-tumor treatments [80,81]. A study with two glioma patients reported that KDTs as a monotherapy seemed ineffective in retarding tumor growth but had more promising effects when combined with standard treatments [82]. These patients received an energy-restricted KD that seemed effective in controlling the progression of primary brain tumors.

### Conclusion

KDTs have diversified to alternative forms for different indications that can be selected based on the specific family and child situation. Recommendations for the use of KDTs have been strengthened by an increasing number of studies testing targeted therapeutic ranges.

### Conflicts of interest

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

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Guillain-Barré syndrome (GBS) is a group of clinical syndromes with acute polyneuropathy secondary to an immune-mediated process, which usually presents with progressive weakness that can involve autonomic, bulbar, and respiratory systems, and reduced or diminished deep tendon reflexes [1]. Since the eradication of polio, GBS has become the most frequent cause of acute or...
subacute flaccid weakness, and reported annual incidence rates of GBS in children range from 0.34 to 1.34 per 100,000 [1-10].

GBS is a clinical diagnosis that can be made when progressive weaknesses in limbs and areflexia or hyporeflexia are present [11]. Other supporting features include progression of symptoms lasting up to 4 weeks, relative symmetry of weakness and sensory loss, less impressive sensory symptoms than weakness if present, pain in back and legs, autonomic dysfunction, absence of fever, albuminocytologic dissociation in cerebrospinal fluid (CSF) studies, and post-gadolinium enhancement of peripheral nerve roots and cauda equina in magnetic resonance imaging (MRI) [12]. Acute inflammatory demyelinating polyneuropathy (AIDP), which targets segments of myelin sheath, is the most common clinical subtype of GBS, along with less common subtypes such as acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN) which target neuronal axon, and Miller-Fisher syndrome that presents with ataxia, areflexia, and ophthalmoplegia [11,13].

The differential diagnosis of the presenting symptoms of GBS—flaccid paralysis, areflexia, or a combination—is extensive including pathology of cerebellum, spinal cord, peripheral nerves, and muscles, and often lead to extensive and costly medical investigations [11]. Children tend to have a better prognosis than adults, with about 80% of children showing full recovery without long-term recurrence [11]. However, a small subset of children experiences residual symptoms that require lengthy and costly rehabilitation. Therefore, in this study, we described clinical characteristics of children with GBS with the aim of searching for findings that can aid in making the diagnosis, and early predictive factors for achieving full recovery.

Materials and Methods

Retrograde chart review was done for previously healthy children of ≤18 years of age diagnosed with GBS and admitted to Pusan National Children’s Hospital between 2009 and 2018. Patients were included in the study when recorded outcome following 6 months after onset were available. Patients who showed disease progression beyond 4 weeks, who had the previous history of other neurologic or chronic systemic diseases, or who were transferred from other hospitals during the course of the disease were excluded.

Diagnosis of GBS was made clinically in patients showing progressive weakness of more than one limb and areflexia/hyporeflexia, according to criteria suggested by Asbury and Cornblath [14]. Detailed neurologic examination findings in a standardized manner, hematological findings, CSF findings, electrophysiological findings, and spine MRI findings were available in all patients.

Antecedent febrile illnesses were all recorded. If the predominant associating symptoms were respiratory symptoms including cough, sputum, and rhinorrhea, it was classified as respiratory antecedent illness. If the predominant accompanying symptoms were gastrointestinal symptoms including vomiting or diarrhea, it was classified as gastrointestinal illness. Details on history of antecedent vaccinations were not complete and therefore were not included.

Hematologic and CSF investigations were all done on the 1st day of admission. Data of neutrophil, lymphocyte, and platelet counts, sodium, albumin, erythrocyte sedimentation rate, C-reactive protein (CRP), creatine kinase, free thyroxine, and thyroid stimulating hormone (TSH) on blood tests, and CSF protein were available in all patients. Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) were calculated by dividing neutrophil or platelet counts by lymphocyte counts, respectively.

Electrophysiological and MRI investigations were all done within 48 hours since admission except for two patients whose spine MRIs were taken 10 and 13 days after admission respectively, due to unstable conditions requiring intensive care unit care. When the above investigations were repeated, initial findings were collected for analysis. However, for classification of subtypes, subsequent electrophysiological abnormal findings were used.

Sub-classifications of AIDP, AMAN, and AMSAN were made based on electrophysiological criteria: (1) AIDP when evidence of demyelination (prolongation of distal latency, slow nerve conduction velocity, f-wave prolongation, conduction block, and temporal dispersion) was observed; (2) AMAN when compound muscle action potential (CMAP) was reduced without evidence of demyelination; and (3) AMSAN when reduced CMAP and sensory nerve action potential amplitudes were observed [15]. Patients were classified as having Miller-Fisher syndrome when they showed low-amplitude sensory nerve action potentials together with the clinical triad of ataxia, areflexia, and ophthalmoplegia [15]. Patients whose electrophysiological results were repeatedly normal were classified as unclassifiable.

Patients were divided into two groups according to their outcome at 6 months—those who achieved full recovery and those with residual motor deficits. Other residual functional deficits present at 6 months were also collected, including bladder dysfunction. Subjective symptoms that are not retractable from records of physical examinations during follow-up visits were not included due to incompleteness of data.

Statistical analysis was performed using SPSS version Subscription 2019 (IBM Co., Armonk, NY, USA). Data from statistical analyses are expressed as medians and interquartile ranges (IQRs) for continuous and ordinal variables and as counts and percentages.
for categorical variables. Univariate analysis for factors affecting functional outcome was done using binary logistic regression. A $P$ value of $< 0.05$ was considered significant.

This study was approved by the Institutional Review Board of Pusan National University Yangsan Hospital (IRB no. 05-2019-176). Written informed consents from patients were waived due to a retrospective nature of the study.

**Results**

A total of 38 children who had been previously healthy and subsequently diagnosed with GBS were subject to this study. The clinical characteristics of the patients are summarized in Table 1. The median age of onset was 4.3 years (IQR, 2.8 to 9.7), and more than half (55.3%) of patients had onset before 5 years of age. Twenty-three (60.5%) were boys, and seasonal distribution showed peak prevalence during winter (42.1%), and least prevalence during autumn (7.9%). Sensory change or pain was accompanied in 19 (50.0%) of patients, whereas autonomic dysfunction was seen in six (15.8%) patients (five with urinary dysfunction and one with both urinary and cardiovascular dysfunctions), and cranial nerve involvements were seen in four patients (10.5%).

Three patients (7.9%) were admitted to the pediatric intensive care unit and were supported with mechanical ventilation. Albuminocytologic dissociations in CSF were present in 14 patients (36.8%) on the first day of admission. Eleven of the 24 patients whose previous CSF findings were negative repeated the CSF exam after 7 to 18 days, which revealed albuminocytologic dissociations in eight patients.

Spine MRIs with T1-weighted, T2-weighted, and post-gadolinium images of the whole spine were done in all patients, and contrast enhancement of spinal nerve roots was present in 27 patients (71.1%). Two patients were evaluated with spine MRI after 48 hours since admission due to their unstable conditions. Of the 36 patients who were evaluated with spine MRI within 48 hours since admission, 25 patients (69.4%) showed contrast enhancement. Subgroup classification showed 23 patients (60.5%) with AIDP, 10 (26.3%) with AMAN, one (2.6%) with AMSAN, and two (5.3%) with Miller-Fisher syndrome. The rest two patients whose initial and follow-up electrophysiological studies were all normal remained as unclassifiable.

When outcomes of 6 months after the onset were assessed, 28 patients (73.7%) were fully recovered without any motor residual symptoms, while 10 patients (26.3%) still had motor residual symptoms. No patient died during 6 months after the onset. Among 10 patients with residual motor weakness, six patients had not achieved independent walking while four patients had weakness in limbs or truncal instability but could walk independently.

### Table 1. Clinical characteristics of 38 children with Guillain–Barré syndrome

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 1</td>
<td>0</td>
</tr>
<tr>
<td>1–4.9</td>
<td>21 (55.3)</td>
</tr>
<tr>
<td>5–9.9</td>
<td>9 (23.7)</td>
</tr>
<tr>
<td>10–18</td>
<td>8 (21.1)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>23 (60.5)</td>
</tr>
<tr>
<td>Girls</td>
<td>15 (39.5)</td>
</tr>
<tr>
<td><strong>Season</strong></td>
<td></td>
</tr>
<tr>
<td>Spring (March–May)</td>
<td>10 (26.3)</td>
</tr>
<tr>
<td>Summer (June–August)</td>
<td>9 (23.7)</td>
</tr>
<tr>
<td>Autumn (September–November)</td>
<td>3 (7.9)</td>
</tr>
<tr>
<td>Winter (December–February)</td>
<td>16 (42.1)</td>
</tr>
<tr>
<td><strong>Antecedent illness</strong></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>21 (55.3)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>4 (10.5)</td>
</tr>
<tr>
<td>Other febrile illnesses</td>
<td>10 (26.3)</td>
</tr>
<tr>
<td>None</td>
<td>3 (7.9)</td>
</tr>
<tr>
<td><strong>Sensory change/Pain</strong></td>
<td>19 (50.0)</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>6 (15.8)</td>
</tr>
<tr>
<td>Cranial nerve involvement</td>
<td>4 (10.5)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>3 (7.9)</td>
</tr>
<tr>
<td>Albuminocytologic dissociation in CSF</td>
<td>14 (36.8)</td>
</tr>
<tr>
<td>Contrast enhancement in spine MRI</td>
<td>27 (71.1)</td>
</tr>
<tr>
<td><strong>Subtypes</strong></td>
<td></td>
</tr>
<tr>
<td>AIDP</td>
<td>23 (60.5)</td>
</tr>
<tr>
<td>AMAN</td>
<td>10 (26.3)</td>
</tr>
<tr>
<td>AMSAN</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Miller-Fisher</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td><strong>Outcome after 6 months</strong></td>
<td></td>
</tr>
<tr>
<td>Full recovery</td>
<td>28 (73.7)</td>
</tr>
<tr>
<td>Residual symptoms</td>
<td>10 (26.3)</td>
</tr>
<tr>
<td>Incomplete independent gait</td>
<td>6 (15.8)</td>
</tr>
<tr>
<td>Motor weakness with ability to walk independently</td>
<td>4 (10.5)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor and sensory axonal neuropathy.
days was given to all patients during admission. In patients who did not show initial response to IVIG with progressing symptoms, plasma exchange was tried in two patients and intravenous methylprednisolone of 30 mg/kg for 3 days was tried in three patients. The two of the three patients who received intravenous methylprednisolone achieved full recovery later, while the rest one patient and two patients who underwent plasma exchange showed residual symptoms after 6 months.

After dividing patients into two groups—one group with 28 patients who achieved the full recovery and another group with 10 patients with residual motor deficits—clinical characteristics were compared between the two groups in search for clinical factors affecting the clinical outcome (Table 2). Among clinical factors listed in Table 2, presence of autonomic dysfunction (odds ratio [OR],

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Full recovery (n = 28)</th>
<th>Functional deficit (n = 10)</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>3.5 (2.6–8.0)</td>
<td>8.1 (3.0–13.4)</td>
<td>1.125 (0.969–1.306)</td>
<td>0.122</td>
</tr>
<tr>
<td>Sex (boys)</td>
<td>18 (64.3)</td>
<td>5 (50.0)</td>
<td>0.556 (0.129–2.394)</td>
<td>0.430</td>
</tr>
<tr>
<td>Seasons</td>
<td></td>
<td></td>
<td>0.518</td>
<td></td>
</tr>
<tr>
<td>Spring</td>
<td>8 (28.6)</td>
<td>2 (20.0)</td>
<td>Reference group</td>
<td></td>
</tr>
<tr>
<td>Summer</td>
<td>7 (25.0)</td>
<td>2 (20.0)</td>
<td>1.143 (0.126–10.386)</td>
<td>0.301</td>
</tr>
<tr>
<td>Autumn</td>
<td>1 (3.6)</td>
<td>2 (20.0)</td>
<td>8.000 (0.45–139.290)</td>
<td>0.301</td>
</tr>
<tr>
<td>Winter</td>
<td>12 (42.9)</td>
<td>4 (40.0)</td>
<td>1.333 (0.196–9.083)</td>
<td>0.464</td>
</tr>
<tr>
<td>Antecedent illness</td>
<td></td>
<td></td>
<td>0.457</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>14 (50.0)</td>
<td>7 (70.0)</td>
<td>Reference group</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>12 (42.9)</td>
<td>2 (20.0)</td>
<td>0.333 (0.058–1.919)</td>
<td>0.457</td>
</tr>
<tr>
<td>None</td>
<td>2 (7.1)</td>
<td>1 (10.0)</td>
<td>1.000 (0.077–13.016)</td>
<td>0.950</td>
</tr>
<tr>
<td>Symptom onset to admission (day)</td>
<td>3.0 (1.0–6.0)</td>
<td>3.5 (2.0–14.0)</td>
<td>1.064 (0.946–1.196)</td>
<td>0.301</td>
</tr>
<tr>
<td>Sensory change/Pain</td>
<td>13 (46.4)</td>
<td>6 (60.0)</td>
<td>1.731 (0.399–7.505)</td>
<td>0.464</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>1 (3.6)</td>
<td>5 (50.0)</td>
<td>27.000 (2.576–282.979)</td>
<td>0.006</td>
</tr>
<tr>
<td>Cranial nerve involvement</td>
<td>3 (10.7)</td>
<td>1 (10.0)</td>
<td>0.926 (0.085–10.085)</td>
<td>0.950</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>1 (3.6)</td>
<td>2 (20.0)</td>
<td>6.750 (0.539–84.464)</td>
<td>0.139</td>
</tr>
<tr>
<td>Contrast enhancement in spine MRI</td>
<td>18 (64.3)</td>
<td>9 (90.0)</td>
<td>5.000 (0.551–45.391)</td>
<td>0.153</td>
</tr>
<tr>
<td>CSF protein (mg/dL)</td>
<td>32.8 (15.0–90.0)</td>
<td>73.0 (19.3–154.4)</td>
<td>1.001 (0.995–1.006)</td>
<td>0.790</td>
</tr>
<tr>
<td>Neutrophil (μL)</td>
<td>5,503 (2,539–8,240)</td>
<td>6,323 (3,097–9,072)</td>
<td>1.000 (1.000–1.000)</td>
<td>0.640</td>
</tr>
<tr>
<td>Lymphocyte (μL)</td>
<td>3,547 (2,165–4,383)</td>
<td>2,787 (1,294–4,637)</td>
<td>1.000 (0.999–1.000)</td>
<td>0.260</td>
</tr>
<tr>
<td>Platelet (109/L)</td>
<td>400 (302–473)</td>
<td>369 (308–513)</td>
<td>1.002 (0.995–1.008)</td>
<td>0.597</td>
</tr>
<tr>
<td>NLR</td>
<td>1.38 (0.47–3.03)</td>
<td>2.43 (0.64–5.27)</td>
<td>1.072 (0.850–1.351)</td>
<td>0.558</td>
</tr>
<tr>
<td>PLR</td>
<td>112.7 (78.5–149.1)</td>
<td>129 (84–256)</td>
<td>1.001 (0.997–1.005)</td>
<td>0.472</td>
</tr>
<tr>
<td>CK (U/L)</td>
<td>74.0 (58.0–121.0)</td>
<td>87.0 (46.5–126.5)</td>
<td>1.004 (0.996–1.013)</td>
<td>0.304</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>137.0 (134.3–138.0)</td>
<td>137.3 (137.5–142.3)</td>
<td>1.269 (0.979–1.645)</td>
<td>0.027</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.55 (4.18–4.70)</td>
<td>4.40 (4.13–4.63)</td>
<td>0.866 (0.346–2.167)</td>
<td>0.759</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>9.0 (4.0–14.0)</td>
<td>11.5 (4.5–46.8)</td>
<td>1.055 (0.948–1.174)</td>
<td>0.324</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.09 (0.01–0.20)</td>
<td>0.12 (0.02–0.48)</td>
<td>14.702 (0.315–685.420)</td>
<td>0.170</td>
</tr>
<tr>
<td>Free T4 (ng/dL)</td>
<td>1.32 (1.14–1.37)</td>
<td>1.25 (1.00–1.42)</td>
<td>0.042 (0.002–23.569)</td>
<td>0.327</td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>1.37 (0.66–2.43)</td>
<td>1.96 (1.09–2.76)</td>
<td>1.406 (0.643–3.073)</td>
<td>0.393</td>
</tr>
<tr>
<td>Subtypes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDP</td>
<td>15 (53.6)</td>
<td>8 (80.0)</td>
<td>Reference group</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>13 (46.4)</td>
<td>2 (20.0)</td>
<td>0.288 (0.052–1.608)</td>
<td>0.156</td>
</tr>
<tr>
<td>CMAP amplitude</td>
<td></td>
<td></td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>Normal or ≥ 50 LLN</td>
<td>22 (78.6)</td>
<td>3 (30.0)</td>
<td>Reference group</td>
<td></td>
</tr>
<tr>
<td>&lt; 50 LLN or absent</td>
<td>6 (21.4)</td>
<td>7 (70.0)</td>
<td>8.556 (1.683–43.495)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

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

OR, odds ratio; CI, confidence interval; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; CK, creatin kinase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; T4, thyroxine; TSH, thyroid stimulating hormone; AIDP, acute inflammatory demyelinating polyneuropathy; CMAP, compound muscle action potential; LLN, lower limit of normal.

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27.000; 95% confidence interval [CI], 2.576 to 282.979; P = 0.006) and absent or decrease in CMAP amplitude to < 50% of lower limit of normal (LLN) (OR, 8.556; 95% CI, 1.683 to 43.495; P = 0.010) were only factors that were significantly associated with increased risk of poor clinical outcome after 6 months.

Multivariate analysis was performed with the parameters that demonstrated P values of < 0.020—age, presence of autonomic dysfunction, use of mechanical ventilation, presence of contrast enhancement on spine MRI, plasma sodium level, plasma CRP level, and CMAP amplitude. Absent or decreased CMAP amplitude was the only clinical factor significantly associated with poor outcome on multivariate analysis (OR, 273.879; 95% CI, 0.417 to 179,920.480; P = 0.039).

Discussion

In this study, apart from findings obtained from detailed history taking and physical examinations, contrast enhancement of peripheral nerve roots and cauda equina on MRI was the most helpful initial finding for making the diagnosis of GBS. Contrast enhancements were seen in 71.1% (27/38) of total patients on their initial spine MRIs, and in 69.4% (25/36) of patients whose MRIs were taken within 48 hours of admission. After 6 months of admission, 26.3% of patients had residual symptoms. When looking at predictive factors of this functional outcome after 6 months, presence of autonomic dysfunction and ≥ 50% decrease in CMAP amplitude from LLN were related to the presence of functional deficit.

Although GBS is the cause for the majority of patients presenting with acute or subacute flaccid paralysis, the incidence is rare as stated before and even rarer in children. The age group known to be most commonly affected in children is 1 to 4 years of age [16]. Around 70% of patients have identified previous infections including cytomegalovirus, Mycoplasma pneumoniae, Epstein-Barr virus, influenza A, Haemophilus influenzae, enterovirus, and Campylobacter jejuni, and the most commonly associated organism identified is Campylobacter jejuni whose antibodies are found in about 40% of patients [3,12,17,18]. Previous studies have shown the high occurrence of GBS winter and summer regarding seasonal distribution which is possibly due to the higher occurrence of associated infections in these seasons, especially gastrointestinal infections during summer [19-22]. In this study, age group of 1 to 4.9 years was most commonly affected (55.3%), as in previous studies. Winter season showed peak incidence (42.1%) in accordance with existing studies, but summer did not show a distinct peak. Also, while higher proportions of patients had the history of antecedent illness (92.1%) than in previous reports, a much smaller subset of patients had gastrointestinal infections (10.5%). Retrospective nature of this study may be attributable to this discrepancy. As laboratory investigations for associated organisms were only done in a small subset of patients included in this study, history from parents or caregivers were analyzed and most parents reported their children to have had “common cold” for previous infections that were mostly of benign nature.

The prognosis of children is known to be better than adults possibly due to shorter nerve length or better nerve regeneration in children, but there is a great paucity of studies regarding the prognosis of GBS in the pediatric population [23]. In a prospective study of 95 children with GBS including two patients later diagnosed with chronic inflammatory demyelinating polyneuropathy, 75% of the children were symptom-free at last follow-up without any mortality (follow-up duration of 10 to 604 days, median 288 days) [24]. In another prospective study with 324 patients, the prognosis was better with 96% of patients achieving independent gait, but also showed 1.5% of mortality [25]. The proportion of patients who achieved independent gait but showed minor functional disability was not mentioned [25]. In this study, 73.7% of patients showed full recovery after 6 months, 15.8% did not achieve independent walking, and 10.5% achieved independent gait but showed minor functional disabilities after 6 months. After 1 year, one patient who could not walk independently achieved independent gait, and two patients with minor motor weakness became symptom-free, resulting in 78.9% of patients with full recovery, and 13.2% of patients without the ability to walk independently after 1 year.

Numerous factors have been suggested as prognostic factors of GBS in studies mostly subjecting adults, and severe deficits at onset, cranial nerve involvement, autonomic nerve involvement, requiring mechanical ventilation, preceding diarrhea, short interval between symptom onset and admission, absent/low amplitude CMAP or axonal lesion patterns in electrophysiological studies are examples of suggested poor prognostic factors [26-28]. Higher age was also a poor prognostic factor in adults [26,27]. However, in children, younger age was associated with poor outcome regarding the achievement of independent gait [25]. In a study which compared the outcome of demyelinating and axonal forms of GBS in children, there was no difference among different subtypes [29]. In an effort for earlier prediction of outcome, biomarkers that associate with the outcome have been searched, and several acute phase markers such as low albumin, low sodium, high NLR, high PLR, and high CRP levels have been shown to be related to poor prognosis of GBS in adults [30-33]. Also, patients with GBS showed lower levels of TSH correlating with disease severity in adults [34]. In this study, autonomic dysfunction and absent or low CMAP of ≥ 50% of LLN were factors associated with poor functional out-
come. None of the acute phase markers such as high NLR, high PLR, high CRP, hyponatremia, low albumin, or low TSH were associated with clinical outcome in this study, suggesting that these markers are not readily applicable prognostic factors in children.

This study has significance as it contributes to the scarce volume of literature describing possible prognostic factors of GBS in children, and also investigated implications for acute phase biomarkers in children. However, it has several limitations including the retrospective nature of this study and the small number of included patients.

Conflicts of interest

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

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Author contributions

Conceptualization: AK. Data curation: SHK, FS, AM, and JK. Formal analysis: AK. Funding acquisition: AK. Methodology: AK. Project administration: AK. Visualization: SHK. Writing-original draft: SHK and AK. Writing-review & editing: AK, YMK, YJL, and SON.

Acknowledgements

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References


Paroxysmal Seizure–Like Activities Caused by Unrecognized Acute Myocarditis Masquerading as Febrile Seizures in Children

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Purpose: Recognition of cardiogenic syncope caused by acute myocarditis masquerading as febrile seizures (FS) in children can be difficult in the emergency department (ED) before a cardiac work-up. We aimed to identify clinical and laboratory characteristics of children with seizure-like activity and fever caused by myocarditis that would enable their condition to be distinguished from benign FS.

Methods: We identified seven children who visited the ED for paroxysmal seizure-like activity with fever and were diagnosed with acute myocarditis between 2012 and 2015, as well as 204 children who were diagnosed with benign FS during the same period. A detailed retrospective review of the medical charts of both groups was conducted.

Results: Age at onset of seizure-like activity was much higher in the myocarditis group than in the FS group (4.4 ± 1.9 years vs. 2.4 ± 1.1 years, P = 0.033). Body temperature at seizure-like activity onset was significantly lower in the myocarditis group than in the FS group (37.9°C ± 0.2°C vs. 38.7°C ± 0.6°C, P < 0.001). Prodromal symptoms were significantly different, with nausea/vomiting (85.7% vs. 1.5%, P < 0.001), abdominal pain (42.9% vs. 0.0%, P = 0.021), and lethargic mentality (57.10% vs. 0.0%, P = 0.015) being more frequent in the myocarditis group. The initial laboratory findings significantly differed between the two groups, with higher levels of liver enzymes, lactate dehydrogenase, creatinine, uric acid, creatine kinase, and potassium in the myocarditis group.

Conclusion: Prodromal symptoms and initial laboratory results were significantly different between the myocarditis and FS groups. A good clinical history and laboratory findings can be helpful for differentiating cardiogenic syncope from benign FS.

Keywords: Child; Myocarditis; Seizures, febrile; Syncope; Arrhythmias, cardiac
Introduction

Among the pediatric population, acute myocarditis is an uncommon but fatal disease. The actual incidence of myocarditis is unknown but is probably underestimated. Most estimates are based on autopsy studies and range from 0.1% to 5.6% in children and adults [1-3]. Some studies have shown peaks in very young children and adolescents [2,4]. In the Emergency Department (ED), early diagnosis of myocarditis in children might benefit from the early administration of intravenous immunoglobulin and inotropic agents, and intervention of mechanical circulatory support [5]. However, diagnosis is difficult because clinical presentation is nonspecific and inconsistent, and misdiagnosis may lead to legal dispute [6].

The most common clinical findings in a case series included tachypnea, intercostal retractions, tachycardia, and grunting, and those symptoms led to 71% of children being misdiagnosed as having either sepsis or pneumonia/asthma [7]. Alternatively, children can present with nausea and vomiting and may be mistakenly diagnosed as having gastroenteritis [8]. Some of these patients may experience unconsciousness with involuntary or seizure-like activities (convulsive syncope) due to generalized cerebral hypoxia of cardiac etiology, which can appear similar to epileptic seizure, leading to a misdiagnosis of epilepsy. In particular, when a young infant or preschool child visits ED presenting with seizure-like activity such as loss of consciousness (LOC) and mild to high fever caused by myocarditis, it may look similar to the symptoms of benign febrile seizure (FS) in children, and a pediatric neurologist should be notified. Unless we consider the possibility of cardiogenic causes, the evaluation and appropriate management of cardiac etiology may be further delayed.

We experienced seven children with acute myocarditis presenting with seizure-like activity and mild to high fever, which was initially considered as possible FS, who were evaluated at the pediatric neurology department before cardiac examination. To the best of our knowledge, there has been no study of the differences in clinical and laboratory findings between children with acute myocarditis with seizure-like activities and FS until now. This study aimed to identify the initial clinical and laboratory characteristics of children with seizure-like activity and fever caused by acute myocarditis that could be differentiated from those of benign FS, except by regular cardiac work-ups such as electrocardiogram (ECG) and echocardiogram.

Materials and Methods

We retrospectively reviewed the medical charts of children who were diagnosed with acute myocarditis and presented a seizure-like activity with mild to high fever as the main complaint, between 2012 and 2015 in a single tertiary care hospital. In considering of the complex FS, we included not only generalized onset seizure but also focal onset seizure such as LOC/impaired awareness. In order to evaluate the children who could suspect the possible FS as well as typical FS, the range of body temperature was more than or 37.7°C. Of 24 children with myocarditis, seven patients (29.2%) visited our ED presenting with seizure-like activity as the main initial symptom. Myocarditis was diagnosed by attending pediatric cardiologists if he/she had clinical symptoms compatible with myocarditis and showed at least one of the following: elevated cardiac enzymes (creatine kinase [CK], CK-MB isoenzyme, or troponin-I [ > 0.1 ng/mL]), cardiomegaly (cardiothoracic ratio > 0.5) on chest radiograph, or impaired heart contractility on echocardiography (ejection fraction < 55%). Exclusion criterion was underlying congenital heart disease, coronary artery anomalies, cardiomyopathy, collagen vascular disease, infection/inflammation originating from the central nervous system (CNS), or heart surgery. Patients older than 6 years were also excluded for comparison with benign FS. These seven children with myocarditis with seizure-like activity and fever were enrolled to the myocarditis-group. They were initially considered as having FS and reported to our neurologist.

During the same period, children who were diagnosed with benign FS were enrolled to the FS-group. Patients with FS were defined by seizures that occurred between the age of 6 and 60 months with a body temperature of ≥ 38°C, which were not caused by CNS infection or any metabolic imbalance [9]. Simple FS was presented with a short generalized onset seizure, of duration of < 15 minutes, not recurring within 24 hours. Complex FS indicated a focal or generalized onset and/or prolonged seizure, of duration of > 15 minutes, recurring more than once in 24 hours, and/or postictal paralysis [9]. Children with status epilepticus, underlying inborn errors of metabolism or chromosomal abnormality, CNS infection and a history of afebrile unprovoked seizures were excluded. Overall, 204 patients were included in the FS-group.

Patients’ demographic profiles, clinical presentations, medical history, vital signs, physical examination findings, and laboratory studies were collected and compared between the myocarditis- and FS-group.

Ethics permission for this study was granted (number: 05-2019-107) by the Institutional Review Board of Pusan National University Yangsan Hospital and fully informed written consent was obtained from each participant.

The SPSS version 19.0 software package (IBM Co., Armonk, NY, USA) was used for statistical analysis of raw scores. The two-
etailed chi-square or Fisher’s exact test was used for analysis of categorical data, and the Student’s t-test for continuous variables with normal distribution. The Mann-Whitney U test was used for continuous variables without normal distribution. In addition to univariate non-parametric statistical tests, Fisher’s exact test and the Wilcoxon signed rank test were used to evaluate significant differences in categorical and continuous variables, respectively. In all analyses, \( P < 0.05 \) was regarded as statistically significant.

**Results**

1. **Clinical features**

The myocarditis- and FS-group included seven and 204 children, respectively. Out of 204 FS, the patients of simple FS and complex FS were 152 (74.5%) and 52 (25.5%). There was no significant difference in gender ratio (boy:girl, 2.7:1 vs. 1.6:1) and mean age (2.3 ± 1.2 years vs. 2.6 ± 1.1 years) between simple and complex FS-group (data not shown). There were two boys (28.6%) in the myocarditis-group, and 140 boys (68.6%) in the FS-group (\( P = 0.070 \)) (Table 1). Children in the myocarditis group (4.4 ± 1.9 years) had a substantially older age at onset of seizure-like activities than those of the FS-group (2.4 ± 1.1 years, \( P = 0.033 \)) (Table 1). Body temperature at seizure-like activities onset was significantly lower in the myocarditis-group than in the FS-group (37.9°C ± 0.2°C vs. 38.7°C ± 0.6°C, \( P < 0.001 \)). Three patients (42.9%) in the myocarditis-group presented seizure-like activities with fever of < 37.8°C, however no children in the FS-group had a seizure with the same degree of fever (Tables 1 and 2). Seizure type was similar between the two groups. Generalized tonic-clonic seizures were the most frequently observed in both myocarditis and FS groups (71.4% and 88.7%, \( P = 0.425 \)). Frequency and duration of seizures were not significantly different between the myocarditis- and FS-groups.

Prodromal symptoms before onset of seizure were statistically different between the two groups (Fig. 1). Nausea/vomiting was the most common symptom in the myocarditis-group (6/7, 85.7%) and was more frequent than in the FS-group (1.5%, \( P < 0.001 \)). Lethargic mentality (57.1% vs. 0.0%, \( P = 0.015 \)) and abdominal pain (42.9% vs. 0.0%, \( P = 0.021 \)) were significantly more common in the myocarditis-group than in the FS-group.

### Table 1. Comparison of clinical and seizure profiles between patients with acute myocarditis and febrile seizure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Myocarditis (n = 7)</th>
<th>Febrile seizure (n = 204)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male:female</td>
<td>2:5</td>
<td>140:64</td>
<td>0.070</td>
</tr>
<tr>
<td>Previous febrile seizure</td>
<td>0</td>
<td>69 (33.8)</td>
<td>0.061</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>4.4 ± 1.9 (0.7–6.0)</td>
<td>2.4 ± 1.1 (0.8–5.0)</td>
<td>0.033</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>37.9 ± 0.2 (37.7–38.2)</td>
<td>38.7 ± 0.6 (38.0–40.0)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>(&lt; 37.8°C)</td>
<td>3 (42.9)</td>
<td>0</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>(\geq 37.8°C)</td>
<td>4 (57.1)</td>
<td>204 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Seizure type</td>
<td></td>
<td></td>
<td>0.425</td>
</tr>
<tr>
<td>Generalized tonic-clonic</td>
<td>5 (71.4)</td>
<td>181 (88.7)</td>
<td></td>
</tr>
<tr>
<td>Focal onset (impaired awareness)</td>
<td>2 (28.6)</td>
<td>23 (11.3)</td>
<td></td>
</tr>
<tr>
<td>Seizure frequency (/day)</td>
<td>2.1 ± 1.5 (1.0–4.0)</td>
<td>1.1 ± 0.3 (1.0–2.0)</td>
<td>0.124</td>
</tr>
<tr>
<td>Seizure duration (min)</td>
<td>1.9 ± 1.8 (0.5–5.0)</td>
<td>2.7 ± 3.6 (0.2–20.0)</td>
<td>0.570</td>
</tr>
</tbody>
</table>

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

*\( P < 0.05 \).

### Table 2. Demographic profiles and clinical presentation of patients with acute myocarditis with seizure-like activities

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>BT (°C)</th>
<th>BP (mm Hg)</th>
<th>HR (/min)</th>
<th>Seizure type</th>
<th>Seizure frequency (/day)</th>
<th>Seizure duration (min)</th>
<th>CTR (CXR)</th>
<th>ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>0.7</td>
<td>37.9</td>
<td>80/50</td>
<td>100</td>
<td>FIA</td>
<td>1</td>
<td>5</td>
<td>0.55</td>
<td>CAVB</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>3.3</td>
<td>38.2</td>
<td>85/65</td>
<td>120</td>
<td>GTC</td>
<td>1</td>
<td>&lt; 1</td>
<td>0.52</td>
<td>ST</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>4.5</td>
<td>38.1</td>
<td>90/55</td>
<td>95</td>
<td>GTC</td>
<td>4</td>
<td>&lt; 1</td>
<td>0.52</td>
<td>ST</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>4.8</td>
<td>37.7</td>
<td>90/60</td>
<td>80</td>
<td>GTC</td>
<td>1</td>
<td>3</td>
<td>0.50</td>
<td>CAVB</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>5.6</td>
<td>38.0</td>
<td>90/60</td>
<td>65</td>
<td>GTC</td>
<td>3</td>
<td>&lt; 1</td>
<td>0.50</td>
<td>CAVB</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>5.9</td>
<td>37.7</td>
<td>90/65</td>
<td>65</td>
<td>GTC</td>
<td>3</td>
<td>1</td>
<td>0.53</td>
<td>CAVB</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>6.0</td>
<td>37.7</td>
<td>85/60</td>
<td>70</td>
<td>FIA</td>
<td>1</td>
<td>3</td>
<td>0.55</td>
<td>CAVB</td>
</tr>
</tbody>
</table>

BT, body temperature; BP, blood pressure; HR, heart rate; CTR, cardio-thoracic ratio; CXR, chest X-ray; ECG, electrocardiography; FIA, focal onset impaired awareness; CAVB, complete atrioventricular block; GTC, generalized tonic-clonic; ST, sinus tachycardia.

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Symptoms of common cold, such as cough or rhinorrhea, were more frequently found in the FS-group than in the myocarditis-group (74.5% vs. 42.9%), but this was not statistically significant ($P = 0.186$).

### 2. Characteristics of initial laboratory results

Initial laboratory findings were significantly different between children in the myocarditis- and FS-groups (Table 3 and Fig. 2). Mean serum levels of chemical profiles were much higher in the myocarditis-group than in the FS-group. Mean levels of aspartate aminotransferase (AST, 322.7 ± 126.3 IU/L vs. 37.1 ± 12.8 IU/L, $P = 0.0001$), alanine aminotransferase (ALT, 149.8 ± 64.0 IU/L vs. 17.1 ± 12.2 IU/L, $P = 0.002$), lactate dehydrogenase (LDH, 1,608.4 ± 972.2 IU/L vs. 570.2 ± 104.8 IU/L, $P = 0.030$), creatinine (0.9 ± 0.3 mg/dL vs. 0.4 ± 0.1 mg/dL, $P = 0.011$), uric acid (8.2 ± 3.0 mg/dL vs. 4.0 ± 0.9 mg/dL, $P = 0.009$), and CK (587.3 ± 252.4 U/L vs.

#### Table 3. Comparison of laboratory results between patients with acute myocarditis and febrile seizures

<table>
<thead>
<tr>
<th>Laboratory findings</th>
<th>Myocarditis (n = 7)</th>
<th>FS (n = 204)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte (x 10^3/µL)</td>
<td>13.2 ± 8.8 (5.3–31.8)</td>
<td>13.5 ± 6.9 (2.5–44.7)</td>
<td>0.897</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.0 ± 1.5 (9.4–14.1)</td>
<td>11.9 ± 1.0 (9.1–13.7)</td>
<td>0.797</td>
</tr>
<tr>
<td>Platelet (x 10^3/µL)</td>
<td>258.7 ± 184.3 (34.0–608.0)</td>
<td>271.0 ± 79.4 (110.0–428.0)</td>
<td>0.866</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>29.2 ± 40.6 (2.0–117)</td>
<td>14.2 ± 13.0 (2.0–56.0)</td>
<td>0.368</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>5.4 ± 5.4 (1.8–17.3)</td>
<td>1.5 ± 1.8 (0.0–8.0)</td>
<td>0.097</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>322.7 ± 1263 (177.0–510.0)</td>
<td>37.0 ± 12.8 (24.0–116.0)</td>
<td>0.001^a</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>149.8 ± 64.0 (79.0–269.0)</td>
<td>17.1 ± 12.2 (8.0–93.0)</td>
<td>0.002^a</td>
</tr>
<tr>
<td>LDH (IU/L)</td>
<td>1,608.4 ± 972.2 (751.0–3,682.0)</td>
<td>570.2 ± 104.8 (396.0–909.0)</td>
<td>0.030^a</td>
</tr>
<tr>
<td>TB (mg/dL)</td>
<td>0.7 ± 0.3 (0.3–1.3)</td>
<td>0.3 ± 0.2 (0.1–1.2)</td>
<td>0.026^a</td>
</tr>
<tr>
<td>DB (mg/dL)</td>
<td>0.3 ± 0.1 (0.1–0.5)</td>
<td>0.1 ± 0.1 (0.0–0.4)</td>
<td>0.008^a</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>20.2 ± 9.5 (8.7–39.5)</td>
<td>12.2 ± 3.6 (7.1–23.3)</td>
<td>0.069</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>0.9 ± 0.3 (0.5–1.5)</td>
<td>0.4 ± 0.1 (0.2–0.7)</td>
<td>0.011^a</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>8.2 ± 3.0 (5.2–14.5)</td>
<td>4.0 ± 0.9 (2.1–6.6)</td>
<td>0.009^a</td>
</tr>
<tr>
<td>Na (mmol/L)</td>
<td>134.5 ± 3.6 (129.0–141.0)</td>
<td>136.0 ± 2.6 (129.0–142.0)</td>
<td>0.051</td>
</tr>
<tr>
<td>K (mmol/L)</td>
<td>4.8 ± 0.4 (4.1–5.2)</td>
<td>4.2 ± 0.4 (3.5–5.2)</td>
<td>0.001^a</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>146.8 ± 46.5 (10.05–231.0)</td>
<td>112.5 ± 20.9 (78.0–179.0)</td>
<td>0.099</td>
</tr>
<tr>
<td>CK (U/L)</td>
<td>587.3 ± 252.4 (319.0–1,032.0)</td>
<td>193.5 ± 210.9 (48.0–993.0)</td>
<td>&lt; 0.001^a</td>
</tr>
</tbody>
</table>

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

FS, febrile seizure; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; TB, total bilirubin; DB, direct bilirubin; BUN, blood urea nitrogen; CK, creatine kinase.

^a$P<0.05$.
vs. 193.5 ± 210.9 U/L, P < 0.001) were significantly higher in the myocarditis-group than in the FS-group. In particular, the minimum AST level in the myocarditis-group (177 IU/L) was higher than the maximum AST level in the FS-group (116 IU/L) (Fig. 2). Hyperkalemia was more obvious in the myocarditis-group than in the FS-group (4.8 ± 0.4 mmol/L vs. 4.2 ± 0.4 mmol/L, P = 0.001). Total blood cell count, ammonia, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), arterial blood gas analysis, glucose, and electrolyte profiles (except for hyperkalemia) were not significantly different between the two groups.

In the myocarditis-group, the mean cardiothoracic ratio on chest X-ray was 0.52 ± 0.24 (Table 2). Two patients (patient 1 and 7) showed definitive cardiomegaly (cardiothoracic ratio ≥ 0.55), and three patients had a mild increase in cardiothoracic ratio (0.52 to 0.53). Conversely, two patients had no cardiomegaly (patient 4 and 5 ratio, 0.5). Initial 12 lead ECG revealed complete atrioventricular block (CAVB) in five (71.4%) and sinus tachycardia in two patients (28.6%). Of the 204 patients in the FS-group, 172 (84.3%) underwent ECG and showed no abnormal heart rhythm.
Discussion

This study investigated a series of seven children, finally diagnosed with acute myocarditis presenting with seizure-like activity (generalized tonic-clonic seizure or LOC/impaired awareness) and fever, who were initially suspected of having benign FS. Children in the myocarditis-group were significantly older and had a lower degree of fever than those in the FS-group. Although the type, duration, and frequency of seizure were similar between the two groups, the prodromal symptoms/signs were very different. The most common preceding symptom/sign was gastrointestinal problems, including nausea/vomiting and abdominal pain, in the myocarditis-group, and symptoms of common cold in the FS-group. We found that the initial laboratory results in ED were remarkably different between the two groups, even though further cardiac evaluation was not performed. Serum levels of AST, ALT, LDH, bilirubin, creatinine, uric acid, CK, and potassium were higher in the myocarditis-group compared to those in the FS-group. If children have specific prodromal symptoms and considerable elevation in the laboratory findings described, we should consider the possibility of seizure-like activities caused by acute myocarditis, even though these seizure-like activities with fever can look similar to those in benign FS.

As high as 20% to 30% of epileptic seizures may have been misdiagnosed [10]. Some patients may have syncope with convolution-like involuntary movements, which can be difficult to clinically differentiate from epilepsy. A Stokes-Adams seizure is defined as sudden collapse into unconsciousness due to a heart rhythm disorder, in which there is a slow or absent pulse resulting in diffuse cerebral hypoxia and consequently syncope and/or convolution [11]. Neglecting a cardiac arrhythmia, which was misdiagnosed as epilepsy, could lead to serious or fatal consequences. In addition, patients may be inappropriately treated with anticonvulsant drugs. Mahoney et al. [12] demonstrated that a Stokes-Adams seizure may be the only clinical manifestation of myocarditis with CAVB. Out of our seven patients with Stokes-Adams seizures, five children showed acute myocarditis with CAVB.

Although many clinicians recognize that resting tachycardia is a common finding of myocarditis due to compensation for congestive heart failure [13], normal heart rates in children with myocarditis were seen in 42% to 66% of patients in two studies [14,15]. For patients with myocarditis with CAVB, bradycardia, rather than tachycardia, is apparent. In our study, none had definitive tachycardia for their age, and in two patients, heart rate was at the low end of the normal range (patient 5 and 6). Since fever and gastrointestinal symptoms usually accelerate a patient’s heart rate, this borderline bradycardia can signal possible cardiac etiology. Carefully and repeatedly checking a child’s heart rate and ECG is very important, especially for those patients with an irregular heart rhythm [15,16]. Findings on ECG in acute myocarditis are nonspecific and include sinus tachycardia, ST-segment and T-wave abnormalities, abnormal axis, heart block, ventricular hypertrophy, atrial enlargement and decreased voltage [13,15,17]. A 12 lead ECG should be recorded as soon as possible after such a series of episodes and should not be discontinued until an event is captured [18]. Two of our patients in the myocarditis-group had sinus tachycardia in the initial ECG.

Cardiomegaly and/or pulmonary edema are common in patients with myocarditis, but are infrequent in myocarditis complicated with CAVB. Suboptimal heart rate may lead to poor cardiac output before the development of congestive heart failure and cardiomegaly [19]. Wang et al. [20] reported an incidence of 22% for cardiomegaly in children with myocarditis with CAVB. Out of our seven patients, significant cardiomegaly (cardiothoracic ratio ≥ 0.55) was observed in 28.6%, and two patients showed no cardiomegaly. It should be considered that cardiomegaly may not be present in all myocarditis patients at the onset of the disease.

Modest elevations in liver enzyme levels are found in patients suffering from passive hepatic congestion [21]. A previous report indicated that an ALT/AST ratio > 1.0 was seen more frequently with enteroviral perimyocarditis in adult patients [22]. We found that serum levels of AST, ALT, LDH, bilirubin, creatinine, uric acid, CK, and K were significantly increased in the myocarditis-group compared with the FS-group. The levels of AST and ALT were > 100 IU/L in all myocarditis patients (except for patient 7, ALT 79 IU/L). In particular, the minimum AST level in the myocarditis-group was higher than the maximum AST level in the FS-group. Elevated levels of AST, ALT and LDH require careful interpretation in patients with myocarditis, because these enzymes are released not only from the liver but also from the skeletal muscles including cardiac muscles. Laboratory cardiac markers including troponin and prohormone of brain natriuretic peptide (proBNP) indicate the presence of myocardial damage and dysfunction in myocarditis [15]. Our myocarditis patients showed highly elevated troponin (17.8 ± 9.2 ng/mL, data not shown) and pro-BNP (7,664 ± 8,895 pg/mL, data not shown), which can recognize that our elevation of AST, ALT, and LDH were associated with cardiac damage as well as hepatic congestion. Furthermore, it should be noted that AST and ALT elevations are not specific to myocarditis and occur in other conditions, such as Kawasaki disease, and in conjunction with many viral illnesses. Kawasaki disease is another confusing situation when investigating myocarditis-related seizures. The incidence of FS in the acute phase of Kawasaki disease could be extremely low (0.18%; 95% confidence interval, 0.02% to 0.66%), confirming the results of one meta-analysis report [23].
Although the number of patients is very small, the pattern of FS in Kawasaki disease was usually clustering seizures, focal seizures, and prolonged unconsciousness after seizures [24]. Kawasaki disease has specific diagnostic criteria, including uncontrolled fever of at least 5 days duration, and unique physical findings, with noticeable laboratory findings. None of our myocarditis-group had suspected Kawasaki disease. Other studies demonstrated that patients with acute myocarditis may have an elevated ESR and CRP as inflammatory indicators [4]. In our study, levels of ESR, CRP, arterial blood gas analysis, ammonia, glucose, and electrolyte profiles (except for hyperkalemia) were not significantly different between the two groups. We presume that the change in liver and renal enzyme, CK, and K levels might be more sensitively influenced than those of inflammatory markers such as ESR and CRP, in the early stage of myocarditis. It is encouraging to know that, when typical or atypical FS in children is clinically suspected, initial laboratory findings, especially serum AST, ALT, LDH, bilirubin, uric acid, K, and CK levels, as well as a chest radiograph and ECG, are likely to distinguish myocarditic Stokes-Adams seizure from FS.

Patients with myocarditis may have only nonspecific complaints. Newborns, infants, toddlers, and preschool children may have a history of respiratory or gastrointestinal infection, anorexia, abdominal pain, poor appetite, vomiting or lethargy, seizure-like activity, sinus tachycardia out of proportion to fever, or syncope, whereas cardiac symptoms may be not prominent [8]. These patients are often diagnosed as having gastroenteritis, pneumonia, asthma, or bronchiolitis. Children with gastrointestinal symptoms are commonly given excessive intravenous fluids, which may exacerbate heart failure. At an older age of >10 years old, children may complain of chest pain, exercise intolerance, myalgias, or palpitations, similar to adults reported in the literature [25]. Well-timed diagnosis remains a challenge as children do not always present with typical signs and symptoms of myocarditis.

Of the varied presentations of myocarditis, CAVB was believed to be an isolated feature, with rapid and full recovery if it was diagnosed early and treated with emergency pacemaker implantation [26]. In our study, all except one patient improved their symptoms and signs of low cardiac output within 1 to 4 days after effective pacemaker implantation. One patient (patient 1) died on the 4th day. He had persistent low cardiac output and developed multiple organ failure due to progressive myocarditis, even after inotropic agent and extracorporeal membrane oxygenation therapy. Unless a high level of alertness is maintained, acute myocarditis may easily be missed and diagnosis may only be obvious in cases where fulminating disease is present.

This study has some limitations. First, the study is based on a retrospective investigation of medical records. Second, we acknowledge that there is a large difference in the number of patients between the two groups to make a comparison with the statistical analysis. This is because myocarditis is very rare, and our study enrolled only the children presenting with seizure-like activities and fever among of them. We did try to use the additional non-parametric statistical methods (Fisher’s exact test and Wilcoxon signed rank test) to increase the reliability of statistical analysis. Third, our study aimed to investigate the clinical and laboratory characteristics of the children with myocarditis, whose initial diagnosis could be mistaken for typical or possible FS. Therefore, not all of our myocarditis patients meet typical FS. Finally, these patients were collected at a single tertiary center and the findings may not be completely representative of the general population. Further population-based studies with a larger number of patients are needed.

In summary, children presenting with fever and Stokes-Adams seizure in our study were not diagnosed as having myocarditis at the initial physician encounter, which highlights the need for clinicians to maintain high level of alertness for myocarditis, even in the absence of clinical findings of congestive heart failure. Prodromal symptoms and initial laboratory results revealed significant differences between the myocarditis- and FS-groups. We suggest that an ECG should be considered as a screening test in all episodes of suspicious benign FS in children, especially in those with significant elevations in laboratory findings, including AST, ALT, LDH, uric acid, and CK.

Conflicts of interest

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

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Author contributions

Conceptualization: SON, JAP, SYB, YMK, and YJL. Data curation: SHJ, HDL, JAP, HK, and YJL. Formal analysis: SHJ, JK, and YMK. Methodology: SON, SYB, HDL, and YJL. Project administration: YJL. Visualization: HK and JK. Writing-original draft: SHJ and AK. Writing-review & editing: AK and YJL.

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References


Prenatal diagnosis of cardiac rhabdomyoma is suggestive of the presence of tuberous sclerosis complex (TSC), which is commonly associated with epilepsy. This study investigated the diagnostic rate of TSC, the incidence and treatment outcomes of epilepsy, and long-term neurodevelopmental outcomes in children with fetal cardiac rhabdomyoma.

Methods: We retrospectively reviewed the medical records of 50 patients with fetal cardiac rhabdomyoma between 1995 and 2017 at the Asan Medical Center Children's Hospital. Twelve patients were excluded because of incomplete data or a follow-up of less than 1 year. Patients' medical records were assessed for the occurrence of epilepsy during follow-up, including treatment and outcomes, electroencephalography and magnetic resonance imaging, genetic analysis findings, and neurodevelopmental status.

Results: Thirty-eight patients (23 males) were diagnosed with TSC. Twenty-eight (73.7%) developed epilepsy. Infantile spasms were observed in 22 patients (78.6%), and 21 (95.5%) received vigabatrin as the first treatment, achieving subsequent freedom from seizures. At the final evaluation, 17 patients (60%) were seizure-free for over 12 months. Seizure remission was not associated with seizure onset age, the presence of cortical tubers, or TSC1/2 mutations. Patients with epilepsy had a higher prevalence of poor neurodevelopmental outcomes than did those without epilepsy (P=0.008).

Conclusion: A high TSC diagnostic rate and a high incidence of early-onset epilepsy were observed in patients with prenatal cardiac rhabdomyoma, and children with TSC and epilepsy showed poor neurodevelopmental outcomes. Therefore, monitoring with electroencephalography follow-up of infants with fetal cardiac rhabdomyoma may be helpful for the early detection and treatment of epilepsy.

Keywords: Tuberous sclerosis; Prenatal diagnosis; Rhabdomyoma; Epilepsy

Introduction

Tuberous sclerosis complex (TSC) is a multi-systemic, autosomal dominant disorder affecting various organs, including the brain, heart, kidneys, liver, eyes, lungs and skin. It is estimated that TSC occurs in about 1 out of 6,000 live births [1].

In fetuses with TSC, cardiac tumors and cortical tubers can be detected in the prenatal period [2-4]. As multimodal imaging has
improved, TSC can be diagnosed prenatally if there are any of the following: cardiac rhabdomyomas, cortical tubers, subependymal nodules, and renal angiomyolipomas [5]. However, the presence of fetal cardiac rhabdomyoma alone is not diagnostic of TSC and the diagnostic rate of TSC in patients with fetal cardiac rhabdomyoma is still unknown [6,7].

Epilepsy is the most common neurologic manifestation in patients with TSC with an incidence of 80% to 90% during the first year of life, with infantile spasms being a very common epilepsy phenotype [4,8]. Early onset and intractable seizures pose a considerable risk of neurodevelopmental and cognitive problems [9-11], and early and immediate seizure control is important in preventing the development of epileptic encephalopathy and intellectual disability [12]. Therefore earlier diagnosis of epilepsy can enable earlier treatment and improve outcomes in children with TSC [10].

This is a retrospective study with long-term follow-up on the natural course of epilepsy and developmental outcomes of patients prenatally diagnosed with cardiac rhabdomyoma. We aimed to describe diagnostic rate of TSC, incidence and treatment outcome of epilepsy, related clinical factors of seizure remission, and long-term neurodevelopmental outcomes in patients prenatally diagnosed with cardiac rhabdomyoma.

Materials and Methods

1. Patients
Between 1995 and 2017 in Asan Medical Center Children's Hospital, 50 patients were prenatally diagnosed with cardiac rhabdomyoma. Of those, 12 patients were excluded because of incomplete medical record data or short-term follow-up less than 1 year and 38 patients were included in this study.

2. Data collection
Of 38 patients, all clinical data were included through March 2017. From our electronic clinical database, we extracted data including demographics (gestational age at birth, birth weight, sex, family history), other TSC manifestations, testing for TSC1 and TSC2 mutation, diagnosis of epilepsy, date of seizure onset, seizure types, presence of hypsarrhythmia, epilepsy treatment (including type and total number of anti-epileptic drugs [AEDs] prescribed during follow-up periods, and non-pharmacologic treatments such as epilepsy surgery, vagus nerve stimulation, and ketogenic diet), and developmental outcomes. The TSC diagnosis followed the recent recommendations from the Tuberous Sclerosis Consensus Conference in 2012 [13]. All patients regularly underwent a complete medical examination, with electroencephalogram (EEG), magnetic resonance imaging (MRI), abdominal sonography, and cardiology/ophthalmic tests. Data on cortical tubers, cardiac complications, and associated anomalies were collected from the final follow-up evaluation. EEG findings at initial seizure onset were classified according to the presence or absence of hypsarrhythmia. Seizure freedom was defined as no seizures occurring for at least 1 year. The definition of well-controlled epilepsy is seizure free at least 1 year at the time of the last evaluation and the definition of uncontrolled epilepsy is sustained seizures within 1 year at final evaluation.

Neurocognitive assessment results were available for all 35 of 38 patients. Abilities were assessed using the Korean Infant and Child Development Test (KICDT; n=24, 68%) and Bayley Scales of Infant Development (BSID-II; n=4, 11%). Children who were older than 5 years of age were tested with the Korean Educational Development Institute-Wechsler Intelligence Scale for Children (KEDI-WISC; n=7, 20%). Those with an intelligence quotient < 70 were considered to have intellectual disability and those with a development quotient < 80 were considered to be delayed in their development. This study was approved by the Institutional Review Board at the Asan Medical Center (IRB No. 2019-1076). Written informed consent by the patients was waived due to a retrospective nature of our study.

3. Data analysis
The independent samples T-test and Mann-Whitney test were used to compare the sizes of the two independent groups of outcome variables. Chi-square tests were used for categorical data regarding the assessment of associated clinical risk factors by using SPSS version 21.0 (IBM, Armonk, NY, USA).

Results

1. Patients characteristics
All 38 patients (23 males and 15 females) who had cardiac rhabdomyoma identified by prenatal sonography were diagnosed with TSC during the follow-up period because they met two major clinical features: cardiac rhabdomyoma and skin manifestations of TSC. Some of them were also diagnosed as TSC with genetic analysis: a mutation of the TSC1 gene was found in three of 38 patients (7.9%) and a mutation in TSC2 in 15 of 38 (39.5%). The median follow-up duration was 4.5 years (range, 1.3 to 26). Five patients (13.2%) were born prematurely (GA < 37 weeks). Most cortical tubers identified on MRI were diffuse, multifocal type (89.5%). However, the presence of fetal cardiac rhabdomyoma alone is not diagnostic of TSC and the diagnostic rate of TSC in patients with fetal cardiac rhabdomyoma is still unknown [6,7].

From our electronic clinical database, we extracted data including demographics (gestational age at birth, birth weight, sex, family history), other TSC manifestations, testing for TSC1 and TSC2 mutation, diagnosis of epilepsy, date of seizure onset, seizure types, presence of hypsarrhythmia, epilepsy treatment (including type and total number of anti-epileptic drugs [AEDs] prescribed during follow-up periods, and non-pharmacologic treatments such as epilepsy surgery, vagus nerve stimulation, and ketogenic diet), and developmental outcomes. The TSC diagnosis followed the recent recommendations from the Tuberous Sclerosis Consensus Conference in 2012 [13]. All patients regularly underwent a complete medical examination, with electroencephalogram (EEG), magnetic resonance imaging (MRI), abdominal sonography, and cardiology/ophthalmic tests. Data on cortical tubers, cardiac complications, and associated anomalies were collected from the final follow-up evaluation. EEG findings at initial seizure onset were classified according to the presence or absence of hypsarrhythmia. Seizure freedom was defined as no seizures occurring for at least 1 year. The definition of well-controlled epilepsy is seizure free at least 1 year at the time of the last evaluation and the definition of uncontrolled epilepsy is sustained seizures within 1 year at final evaluation.

Neurocognitive assessment results were available for all 35 of 38 patients. Abilities were assessed using the Korean Infant and Child Development Test (KICDT; n=24, 68%) and Bayley Scales of Infant Development (BSID-II; n=4, 11%). Children who were older than 5 years of age were tested with the Korean Educational Development Institute-Wechsler Intelligence Scale for Children (KEDI-WISC; n=7, 20%). Those with an intelligence quotient < 70 were considered to have intellectual disability and those with a development quotient < 80 were considered to be delayed in their development. This study was approved by the Institutional Review Board at the Asan Medical Center (IRB No. 2019-1076). Written informed consent by the patients was waived due to a retrospective nature of our study.

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Results
tricular outflow tract obstruction (LVOTO), tetralogy of fallot (TOF). Patient with LVOTO had partial tumor resection operation and patient with TOF had TOF correction operation because of their structural anomalies. Spontaneous tumor regression occurred in 10 patients (35.7%). Baseline demographics are shown in Table 1.

2. Epilepsy characteristics and related clinical risk factors
With a median follow-up of 4.5 years (range, 1.3 to 26), 28 patients (73.7%) developed epilepsy and mean age at seizure onset was 9 months (range, 0.13 to 32). At the time of the last evaluation, 17 patients (60.7%) were seizure-free for longer than 12 months. Infantile spasms were observed in 22 patients (78.6%), 21 of whom (95.5%) received vigabatrin as the first treatment and achieved subsequent seizure freedom. Epilepsy characteristics are shown in Table 2.

Table 2 also shows the comparison of clinical characteristics between patients with well-controlled epilepsy (seizure free at last evaluation) and patients with uncontrolled epilepsy (sustained seizures at final evaluation). Among 28 patients who developed epilepsy, there were 17 (60.7%) with well-controlled epilepsy and 11 (39.3%) with uncontrolled epilepsy at the final evaluation. Apart from the number of AEDs used, there was no difference in clinical characteristics between well-controlled and uncontrolled patients (1.2 ± 0.728 for well-controlled patients, 3.2 ± 0.982 for uncontrolled patients).

### Table 1. Patient characteristics (n=38)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity (&lt; gestational age 37 weeks)</td>
<td>5 (13.2)</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.21 (2.28–4.16)</td>
</tr>
<tr>
<td>Male sex</td>
<td>23 (60)</td>
</tr>
<tr>
<td>Family history</td>
<td>3 (7.9)</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td></td>
</tr>
<tr>
<td>Multiple rhabdomyoma</td>
<td>38 (100)</td>
</tr>
<tr>
<td>Arrhythmia (PVC, PSVT, WPW syndrome)</td>
<td>6 (15.8)</td>
</tr>
<tr>
<td>Structural anomalies (LVOTO, TOF)</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td>Associated anomalies</td>
<td></td>
</tr>
<tr>
<td>Skin (hypopigmented macule)</td>
<td>38 (100)</td>
</tr>
<tr>
<td>Renal (cyst or AML)</td>
<td>17 (44.7)</td>
</tr>
<tr>
<td>Retina (hamartoma)</td>
<td>17 (44.7)</td>
</tr>
<tr>
<td>Delayed development or intellectual disability</td>
<td>19 (50)</td>
</tr>
<tr>
<td>Cortical tuber on brain MRI</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Focal</td>
<td>3 (7.9)</td>
</tr>
<tr>
<td>Diffuse, multifocal</td>
<td>34 (89.5)</td>
</tr>
<tr>
<td>Genetics</td>
<td></td>
</tr>
<tr>
<td>No mutation</td>
<td>4 (10.5)</td>
</tr>
<tr>
<td>TSC1 mutation</td>
<td>3 (7.9)</td>
</tr>
<tr>
<td>TSC2 mutation</td>
<td>15 (39.5)</td>
</tr>
<tr>
<td>Unknown/not-defined</td>
<td>16 (42.1)</td>
</tr>
</tbody>
</table>

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

### Table 2. Comparison of clinical characteristics between well-controlled and uncontrolled epileptic patients with tuberous sclerosis complex

<table>
<thead>
<tr>
<th>Total patients (n=28)</th>
<th>Well controlled (n=17, 60.7%)</th>
<th>Uncontrolled (n=11, 39.3%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at seizure onset (mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 12</td>
<td>11 (64.7)</td>
<td>9 (81.8)</td>
<td>0.416</td>
</tr>
<tr>
<td>≥ 12</td>
<td>6 (35.3)</td>
<td>2 (18.2)</td>
<td></td>
</tr>
<tr>
<td>History of seizure type</td>
<td></td>
<td></td>
<td>0.355</td>
</tr>
<tr>
<td>Spasm</td>
<td>12 (70.1)</td>
<td>10 (90.9)</td>
<td></td>
</tr>
<tr>
<td>Non-spasm (focal or other generalized)</td>
<td>5 (29.4)</td>
<td>1 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Initial EEG at diagnosis</td>
<td></td>
<td></td>
<td>0.419</td>
</tr>
<tr>
<td>Hypsarrhythmia</td>
<td>6 (35.3)</td>
<td>2 (18.2)</td>
<td></td>
</tr>
<tr>
<td>Non-hypsarrhythmia (multi–focal)</td>
<td>11 (64.7)</td>
<td>9 (81.8)</td>
<td></td>
</tr>
<tr>
<td>Cortical tuber on brain MRI</td>
<td></td>
<td></td>
<td>0.488</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>1 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>1 (5.9)</td>
<td>1 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Diffuse, multifocal</td>
<td>16 (94.1)</td>
<td>9 (81.8)</td>
<td></td>
</tr>
<tr>
<td>Genetics</td>
<td></td>
<td></td>
<td>0.268</td>
</tr>
<tr>
<td>No mutation</td>
<td>1 (12.5)</td>
<td>1 (12.5)</td>
<td></td>
</tr>
<tr>
<td>TSC1 mutation</td>
<td>2 (25)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>TSC2 mutation</td>
<td>5 (62.5)</td>
<td>7 (87.5)</td>
<td></td>
</tr>
<tr>
<td>Total treatment duration (yr)</td>
<td>7.1 (0.3–26.1)</td>
<td>5.6 (1.1–15.8)</td>
<td>0.560</td>
</tr>
<tr>
<td>No. of AEDs used</td>
<td>1.2 ± 0.728</td>
<td>3.2 ± 0.982</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

EEG, electroencephalogram; MRI, magnetic resonance imaging; TSC, tuberous sclerosis complex; AED, anti-epileptic drug.
trolled patients, P < 0.001). Seizure remission was not associated with age at seizure onset, the presence of cortical tubers, or TSC1/2 mutations. One patient received vagus nerve stimulation (n=1) as a non-pharmacologic treatment.

A total of 14 different AEDs were used and some patients received multiple AEDs. Fig. 1 shows AED types used between patients with well-controlled and uncontrolled epilepsy. The most common AEDs among patients with well-controlled epilepsy were vigabatrin (n=13), and zonisamide (n=5), while patients with uncontrolled seizure received clobazam (n=8), oxcarbazepine (n=6), topiramate (n=6), and rufinamide (n=2).

3. Neurodevelopment outcome

With a median follow-up of 4.5 years (range, 1.3 to 26), 19 of 38 (50%) patients were identified as having delayed development or an intellectual disability (Table 1). Eighteen of 28 patients (64.3%) with epilepsy were found to have delayed development or intellectual disability. Among the 10 patients without epilepsy, a smaller proportion (10%) had delayed development or intellectual disability (Fig. 2). Epileptic patients were more likely to have poor neuro-

![Fig. 1. Anti-epileptic drugs (AEDs) used in patients with tuberous sclerosis complex and epilepsy whether seizures were well-controlled or uncontrolled. A total of 14 different AEDs were used and some patients received multiple AEDs. The most common AEDs among patients with well-controlled epilepsy were vigabatrin (n=13), and zonisamide (n=5), while patients with uncontrolled seizure received clobazam (n=8), oxcarbazepine (n=6), topiramate (n=6), and rufinamide (n=2).](https://doi.org/10.26815/acn.2019.00185)

![Fig. 2. Neurodevelopmental outcomes in non-epilepsy group and epilepsy group. Nineteen of 38 (50%) patients were identified as having delayed development or an intellectual disability. Eighteen of 28 patients (64.3%) with epilepsy were found to have delayed development or intellectual disability. Among the 10 patients without epilepsy, one patients (10%) had delayed development or intellectual disability.](https://doi.org/10.26815/acn.2019.00185)
developmental outcome \((P=0.008)\). Among epileptic patients, children with delayed development had longer periods of sustained seizure \((0.44 \pm 0.578\) years for children with normal development, \(4.12 \pm 4.468\) years for children with delayed development, \(P=0.018)\).

**Discussion**

TSC is an autosomal dominant congenital syndrome and appears in various phenotypes caused by mutations in one of the tumor suppressor genes, TSC1 or TSC2 [14]. TSC is known to have benign tumors in various tissues and neurological manifestations such as epilepsy, mental retardation, and behavioral problems [8]. In recent decades, with developing imaging techniques, TSC can be diagnosed in the prenatal period if there are any of the following: cardiac rhabdomyomas, cortical tubers, subependymal nodules, or renal angiomyolipomas [5]. Among those, multiple cardiac rhabdomyomas are the most common prenatal sign of TSC [2]. In this study, we selected patients diagnosed with fetal cardiac rhabdomyoma in a single tertiary hospital and analyzed their follow-up data. All 38 patients who had prenatal cardiac rhabdomyoma were eventually diagnosed with TSC during the follow-up period. Given the high rate of diagnosis of TSC following presentation with prenatal cardiac rhabdomyoma, it seems that more emphasis on the surveillance for other TSC features in these patients may be warranted [7].

Epilepsy is a common neurological symptom and this study also showed that TSC patients are at high risk for developing epilepsy [4,8]. In our study, 28 of 38 patients (73.7%) developed epilepsy with a mean age at seizure onset of 9 months (range, 0.13 to 32). This is similar figure as those given by Jozwiak et al. [15] and Wu et al. [16], and tuberous sclerosis registry to increase disease awareness (TOSCA) study on large population also reported that epilepsy developed in 86.3% of patients and 79.3% were diagnosed with epilepsy before 2 years [17]. In addition, a high incidence of infantile spasms (78.6%) was observed in this study, which is different from the result of the TOSCA study: 38.9% presented with infantile spasms and 67.5% with focal seizures [17]. Twenty-one of patients with infantile spasms (95.5%) received vigabatrin as the first treatment and achieved subsequent seizure freedom. At the TSC Consensus Meeting for Subependymal Giant Cell Astrocytoma and Epilepsy Management, the latest recommendations for treatment of epilepsy in TSC is vigabatrin as a first line monotherapy for both infantile spasms and focal seizures [18]. Vigabatrin is a highly selective inhibitor of gamma-aminobutyric acid (GABA) transaminase and epileptogenesis in TSC is associated with reduced activity of GABA inhibition. For this reason, vigabatrin is thought to be particularly effective against epilepsy caused by TSC [19-21]. Although use of vigabatrin was not associated with seizure freedom in this cohort, the use of vigabatrin should be considered in young children with TSC. Many previous studies showed early control of seizures might improve cognitive and behavioral outcomes [10,11,22]. Most of children in the cohort used vigabatrin as the first AED for their seizure control and achieved good outcomes. Visual field defects have been reported as a side effect of vigabatrin [23-25], but this has been reported to be less common in young children than in adults and are relatively safe for use in children [21].

In this study, seizure remission was not associated with age at seizure onset, the presence of cortical tubers, or TSC1/2 mutations, probably due to small number of patients. Previous study showed that patients with later onset seizures had longer periods of seizure freedom [12,22]. Samir et al. [14] observed that early seizure onset (<6 months) is related with poor seizure outcomes. Jansen et al. [26] reported that patients with TSC2 mutations have more intractable seizures than those with TSC1 mutations. An increased number of tubers has also been associated with poor seizure control [11,27]. Other studies, however, have suggested no significant association between higher tuber count and poor seizure control [28,29].

The rate of intellectual disability in patients with TSC is 40% to 70%, while severe intellectual disability has been reported as high as 30% to 45% of these patients [30-32]. A previous large series of 160 patients from Mayo Clinic also showed a strong association between intellectual disability and epilepsy [33]. In our cohort of patients who were prenatally diagnosed with cardiac rhabdomyoma, patients with epilepsy tend to have poor neurodevelopmental outcomes; this finding is consistent with earlier studies suggesting that epilepsy is an important risk factor for developmental delay [30-32,34,35]. Previous studies have shown that EEG abnormalities precede epilepsy onset in TSC patients [1] and improved developmental outcomes were observed when the anti-epileptic treatment was given to infants before the onset of clinical seizures [15]. Wu et al. [16] and Whitney et al. [36] also showed prospectively evaluated usefulness of EEG surveillance for prediction of epilepsy in TSC. This finding suggests that close EEG follow-up of patients with fetal cardiac rhabdomyoma can be used lead to better outcomes in these patients.

This study analyzed long-term follow-up data of a relatively large population of children with fetal cardiac rhabdomyoma, a rare disease. Due to the retrospective nature of this study, evaluation schedules, clinical follow-up, and developmental screening tests were variable between patients. Further, large proportion of the patients were lost to follow-up.

In conclusion, all patients in this study with prenatal cardiac
rhabdomyoma were eventually diagnosed with TSC, either clinically or genetically during the follow-up period. Although it is controversial as to whether all patients who have prenatal cardiac rhabdomyoma will also be diagnosed with TSC, it is clear that these patients are high risk group for TSC and should be monitored for other clinical manifestations of TSC. In this study, epilepsy appears in 78.7% of patients with TSC, most commonly before first year of age. About 80% of children with epilepsy in TSC patients present with infantile spasms, most of them were treated with vigabatrin and had good responses like previous studies. In this cohort, development of epilepsy was also associated with poor neurodevelopmental outcomes. Therefore, all infants prenatally diagnosed with cardiac rhabdomyoma have high potential of being diagnosed with TSC and should be closely monitored with EEG follow-up for the early diagnosis and treatment of epilepsy.

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

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References


Experience of a Single Center in Treating Multiple Manifestations of Tuberous Sclerosis Complex with Everolimus

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Introduction

Tuberous sclerosis complex (TSC) is a disease in which hamartomas grow in the kidney, brain, heart, liver, and skin, resulting from the decreased or absent expression of the TSC1 (hamartin) or TSC2 (tuberin) genes [1,2]. The hamartin-tuberin complex serves to inhibit mechanistic target of rapamycin complex 1 (mTORC1), and the loss of the complex activates mTORC1, leading to aberrant signals and tumor growth [3]. Rapamycin (sirolimus), a macrolide derived from Streptomyces hygroscopicus, and its analog molecules, including everolimus, are inhibitors of the mammalian target of rapamycin (mTOR) [4]. These drugs combine with a cytosolic...
protein, FK506-binding protein 12 (FKBP-12), across the cell membrane to form an FKBP-12-rapalog complex, which inhibits the ability of mTORC1 to interfere with proliferation and cellular metabolism of protein synthesis, neoangiogenesis, glycolysis, and proliferation [4]. Long-term use of these drugs also inhibits mTORC2, which affects both T and B cells, resulting in immunosuppression and glucose intolerance [4,5]. Everolimus is more specific to mTORC1 than sirolimus, and therefore, causes fewer metabolic side effects [5].

In 1999, the Food and Drug Administration (FDA) and the European Medical Agency (EMA) approved sirolimus to prevent rejection of kidney transplants in children aged 13 or older. The EXIST-I and II studies (examining everolimus in a study of TSC) showed that everolimus elicited a response rate superior to placebo for subependymal giant cell astrocytoma (SEGA), renal angiomyolipoma (AML), and skin lesions in patients with TSC [6,7]. The interim analysis of the subsequent open-label extension phase also showed the stability of everolimus effects over time [8-10]. The U.S. FDA currently approves everolimus for adult patients with renal AML that does not require immediate surgery and patients aged 3 years or older with SEGA requiring therapeutic intervention who are not candidates for curative surgical resection. Furthermore, the EMA approved everolimus for add-on treatment in patients aged 2 years or older with seizures associated with TSC that have not responded to other treatments.

In Korea, there are several case reports about the use of everolimus targeted to renal AML or SEGA, but no large clinical study about efficacy and tolerability has been conducted to date. The aim of this study is to describe our center’s experience with everolimus in the management of multiple manifestations of TSC.

Materials and Methods

Using the Asan Medical Center’s in-house research database (ABLE) with the keywords “tuberous sclerosis AND everolimus,” all TSC patients who were treated with everolimus in Asan Medical Center were retrieved. Twenty patients received everolimus for TSC manifestations from 2013 to February 2019. A diagnosis of TSC was made according to the 2012 International TSC Consensus Conference [11]. Everolimus was prescribed according to the Korean FDA approval. However, one patient was enrolled in the EXIST-III study that evaluated everolimus for intractable seizures, and four neonates were treated with off-label use for cardiac rhabdomyoma (RHM) that caused cardiac outflow obstruction or cardiac arrhythmias. These patients were included in the patient cohort of this study.

The standard initial dose of everolimus was 4.5 mg/m² administered as a single dose. In children and adolescents, everolimus was administered as 2.5, 5, or 7.5 mg once daily in patients with body surface areas of 0.5 to 1.2, 1.3 to 2.1, and > 2.2 m², respectively. For adults, 10 mg of everolimus once daily was prescribed for the initial dose. The dose was titrated in 2.5 mg increments or decrements to reach the trough level of 5 to 15 ng/mL. In neonates, the initial dose of everolimus was 0.0625 to 0.25 mg depending on body surface area, and the dose was titrated using the trough level weekly. The neonatal dose was estimated to be 0.65 mg/m²/day based on previous studies [12].

The effects of everolimus were evaluated by routine check-ups and imaging studies for the kidney, brain, and heart, which were performed every 3 to 12 months. To monitor the side effects of everolimus, complete blood counts, liver and kidney function tests, serum triglycerides, cholesterol, and drug trough levels were measured.

This study was approved by the Institutional Review Board (IRB) of Asan Medical Center (IRB 2019-1292). Written informed consent was waived due to the retrospective nature of the study but was obtained from each of the neonatal parents.

Results

1. Baseline characteristics

Twenty patients were treated with everolimus in TSC during the trial period. Table 1 summarizes the clinical and genetic data for enrolled patients. Thirteen patients were male, and their median age at initiation of treatment was 25.6 years (range, 0 to 57.2). The median period of everolimus treatment was 87.6 weeks (range, 0.4 to 289.6). Genetic analysis was carried out in 12 of the 20 cases, and seven patients had a mutation in TSC2, and no patients had a TSC1 mutation.

Fifteen of twenty patients (75.0%) had renal AMLs. Neuroimaging revealed tubers in 11/20 patients (55.0%), subependymal nodules (SENs) in 12 (60.0%), and SEGA in seven patients (35.0%). Overall, 10/20 patients (50.0%) experienced epileptic seizures, and among these, three patients presented with intractable epilepsy. Cardiac RHM were present in six patients. Retinal hamartomas were present in three individuals. Dermatologic manifestations, including facial angiofibroma, were found in 14 patients.

The reasons for initiation of mTOR inhibitor treatment were renal AML in 15/20 cases (75.0%), renal AML and SEGA in four (20.0%), refractory epilepsy in one (5.0%), and symptomatic cardiac RHM and/or arrhythmia in four (20.0%) (Table 1 and Fig. 1).

2. Everolimus exposures

Adolescents and adults received everolimus in doses ranging from
5 to 10 mg daily (mean, 7.1), while newborns up to 3 months received everolimus in doses ranging from 0.0625 to 0.5 mg daily. Treatment was ongoing in 12 of 20 patients at the time of this writing, and three patients discontinued everolimus after successful reduction of renal AML or cardiac RHM. Early withdrawal of everolimus was observed in five patients including four patients with side effects, and one patient died from disease progression during the treatment.

3. Renal angiomyolipoma response

Fifteen patients were diagnosed with renal AML, all of which were bilateral and multifocal. Eight patients had received interventional therapy including selective angioembolization prior to everolimus therapy and 12 had received everolimus for more than 1 year. Before treatment, the mean longest diameter of largest AML was 9.2 ± 4.4 cm (range, 3.4 to 16.4). After a mean of 106 weeks of drug

---

**Table 1. Clinical data of mammalian target of rapamycin inhibitor therapy on TSC-related manifestations**

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Sex</th>
<th>Age at inclusion (yr)</th>
<th>Mutation</th>
<th>Renal AML</th>
<th>SEGA</th>
<th>Cardiac RHM</th>
<th>Other manifestations</th>
<th>Duration of drug (wk)</th>
<th>Maintenance dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>57.2</td>
<td>NA</td>
<td>●</td>
<td></td>
<td></td>
<td>SEN, facial angiofibroma</td>
<td>134 (stop; drug-induced ILD)</td>
<td>7.5</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>49.6</td>
<td>TSC2</td>
<td>●</td>
<td></td>
<td></td>
<td>SEN, tubers, epilepsy, pul LAM</td>
<td>144</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>36</td>
<td>TSC2</td>
<td>●</td>
<td></td>
<td></td>
<td>SEN, tubers, hepatic AML, facial angiofibroma</td>
<td>96 (stop; persistent fever)</td>
<td>7.5</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>40.6</td>
<td>TSC2</td>
<td>●</td>
<td></td>
<td></td>
<td>Tubers, epilepsy, hepatic AML, facial angiofibroma</td>
<td>73 (stop; successful reduction)</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>31.1</td>
<td>NA</td>
<td>●</td>
<td></td>
<td></td>
<td>SEN, tubers, pul LAM, hepatic AML, facial angiofibroma</td>
<td>89</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>31</td>
<td>TSC2</td>
<td>●</td>
<td></td>
<td></td>
<td>Facial angiofibroma</td>
<td>70</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>42.5</td>
<td>NA</td>
<td>●</td>
<td></td>
<td></td>
<td>Tubers, facial angiofibroma</td>
<td>62</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>25.7</td>
<td>NA</td>
<td>●</td>
<td></td>
<td></td>
<td>SEN, tubers, epilepsy, pul LAM, retinal hamartoma, facial angiofibroma</td>
<td>55</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>20.6</td>
<td>NA</td>
<td>●</td>
<td></td>
<td></td>
<td>SEN, tubers, epilepsy, facial angiofibroma</td>
<td>31</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>23.9</td>
<td>NA</td>
<td>● ●</td>
<td></td>
<td></td>
<td>SEN, tubers, epilepsy, hepatic AML, retinal hamartoma, facial angiofibroma</td>
<td>284</td>
<td>5</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>33.9</td>
<td>NA</td>
<td>● ●</td>
<td></td>
<td></td>
<td>Renal AML, epilepsy, facial angiofibroma, shagreen patch, hypopigmented macule</td>
<td>290</td>
<td>5</td>
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<tr>
<td>12</td>
<td>M</td>
<td>27.4</td>
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<td>● ●</td>
<td></td>
<td></td>
<td>SEN, tubers, intractable epilepsy, facial angiofibroma</td>
<td>89</td>
<td>10</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>31.9</td>
<td>NA</td>
<td>● ●</td>
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<td></td>
<td>Hepatic AML, facial angiofibroma</td>
<td>68</td>
<td>10</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>20.3</td>
<td>NA</td>
<td>● ●</td>
<td></td>
<td></td>
<td>SEN, tubers, epilepsy, facial angiofibroma</td>
<td>47</td>
<td>10</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>25.4</td>
<td>NA</td>
<td>● ● ●</td>
<td></td>
<td></td>
<td>SEN, tubers, intractable epilepsy, MMPH, hepatic AML, facial angiofibroma</td>
<td>65</td>
<td>10</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>14.6</td>
<td>NA</td>
<td>● ●</td>
<td></td>
<td></td>
<td>Intractable epilepsy, SEN, retinal hamartoma, facial angiofibroma</td>
<td>114 (stop; emotional instability)</td>
<td>10</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>0</td>
<td>TSC2</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td>31 (stop; successful size reduction)</td>
<td>0.5</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>0</td>
<td>TSC2</td>
<td>●</td>
<td></td>
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<td>8 (stop; neutropenia)</td>
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</tr>
<tr>
<td>19</td>
<td>M</td>
<td>0</td>
<td>TSC2</td>
<td>● SEN</td>
<td></td>
<td></td>
<td></td>
<td>2 (stop; successful size reduction)</td>
<td>0.25</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>0</td>
<td>NA</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td>0 (stop; death d/t RV obliteration)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

TSC, tuberous sclerosis complex; AML, angiomyolipoma; SEGA, subependymal giant cell astrocytoma; RHM, rhabdomyoma; NA, not available; SEN, subependymal nodule; ILD, interstitial lung disease; pul, pulmonary; LAM, leioangiomyoma; MMPH, multifocal micronodular pneumocyte hyperplasia.

5 to 10 mg daily (mean, 7.1), while newborns up to 3 months received everolimus in doses ranging from 0.0625 to 0.5 mg daily. Treatment was ongoing in 12 of 20 patients at the time of this writing, and three patients discontinued everolimus after successful reduction of renal AML or cardiac RHM. Early withdrawal of everolimus was observed in five patients including four patients with side effects, and one patient died from disease progression during the treatment.

**Fig. 1.** Reasons for the initiation of treatment with everolimus, an mammalian target of rapamycin inhibitor. AML, angiomyolipoma; RHM, rhabdomyoma; SEGA, subependymal giant cell astrocytoma.
administration, all of the AML nodules reduced in size, with the largest mass decreasing to 6.9 ± 4.5 cm (range, 2.4 to 14.3) (Fig. 2). In two patients (16.7%) the size of the AML decreased by > 50%, four (33.3%) experienced decreases of 25% to 50%, five (41.7%) experienced decreases of 10% to 25%, and none had progression of tumors (Fig. 3).

Fig. 2. Tuberous sclerosis complex-related renal angiomyolipoma (AML) size changes under everolimus treatment. Fifteen patients were diagnosed with renal AML, and 8 of them had previous AML therapy, including percutaneous embolization (EMB) or radiofrequency ablation (RFA) due to ruptured AML or large mass size. The data for Patient #11 were not included due to the absence of follow-up imaging. The mean longest diameter of the largest AML was 9.2 ± 4.4 cm (range, 3.4 to 16.4). After everolimus treatment for a mean duration of 106 weeks, the size of renal AML decreased to 6.9 ± 4.5 cm (range, 2.4 to 14.3). NA, not available.
4. Subependymal giant cell astrocytoma lesion response

Seven of twenty patients (35.0%) developed SEGA during the observation period. Four of seven patients with SEGA had previous surgical treatment. With the exception of two patients (Patients #14 and #16) who had no follow-up data, the largest size of SEGA before drug use was $19.2 \pm 8.9$ mm (range, 10 to 33) and decreased to $12.6 \pm 4.5$ mm (range, 7 to 18) after everolimus treatment for a mean duration of 106 weeks (Fig. 4).

Four of seven patients were treated with everolimus due to growing or symptomatic SEGA. These four patients experienced a 25% to 50% size reduction. A significant reduction of SEGA size was documented by magnetic resonance imaging after a short follow-up of 2 and 3 months of treatment, respectively (Fig. 5).

5. Cardiac rhabdomyoma response

Six of twenty patients (30.0%) showed cardiac RHM at birth. In four of these six cases, everolimus was initiated due to obstruction of cardiac outflow or fatal cardiac arrhythmias refractory to treatment with atenolol or isoproterenol in neonatal periods. The patients received 0.0625 to 0.25 mg of everolimus as a starting dose and were titrated to reach a trough level of 5 to 15 ng/mL.

One patient (Patient #20) died due to a RHM-induced right ventricle obstruction within 20 days of birth and treatment with everolimus. In the remaining three cases, initiation of everolimus therapy led to a rapid decrease of associated RHM size and control of cardiac arrhythmias. Discontinuation of everolimus caused regrowth of the cardiac RHM (Fig. 6).

6. Epilepsy response

Epilepsy was diagnosed for 10/20 patients (50.0%). Each of these 10 of these patients had cortical tubers, SEN, or SEGA. Three patients had treatment-resistant epilepsy at the start of everolimus
treatment, and one patient (Patient #16) who was included in the EXIST-III study became almost seizure-free on a combination therapy consisting of everolimus, lamotrigine, topiramate, and clobazam. Two patients (Patients #12 and #15) who had previously experienced focal seizures that were refractory to two to three antiepileptic drugs, experienced a 50% reduction in seizure frequency with everolimus treatment. However, Patient #16 experienced seizure recurrence after discontinuation of everolimus due to an adverse event (emotional instability).

7. Skin lesion response
Skin lesions (facial angiofibroma) associated with tuberous sclerosis were present at baseline in 14 patients. Nine of 14 patients (64.3%) showed markedly decreased skin lesions after everolimus administration.

8. Safety outcomes
Adverse events occurred in 17 cases (85.0%) with a median of 3.2 adverse events (range, 0 to 11) per individual, including mild transient mucositis (10 patients); increased serum cholesterol and triglycerides (six patients); hypertension (five patients); headache (four patients); gastrointestinal troubles such as nausea, vomiting, and diarrhea (three patients); and worsening of acne or folliculitis (three patients). Severe adverse events resulting in discontinuation or dose modification were reported in five patients, including drug-induced interstitial lung disease, persistent fever, neutropenia, emotional instability, and severe oral ulcer (Fig. 7).

Discussion
We collected data from 20 TSC patients from a single tertiary center in Korea. Treatment was initiated for renal AMLs (15/20, 75.0%), renal AML and SEGA (4/20, 20.0%), cardiac RHM (4/20, 20.0%), and intractable epilepsy (1/20, 5.0%). Therapeutic benefits following everolimus treatment were observed as decreases in renal AML, SEGA, and cardiac RHM size, and reductions in...
arrhythmia or seizure frequency, or improvements in skin lesions. Everolimus therapy was well tolerated. Treatment is currently ongoing in 12/20 patients (60.0%), and another three patients are stable with reduced tumor burden (renal AML in one case; cardiac RHM in two cases) even after discontinuing everolimus treatment. To the best of our knowledge, this is the largest cohort study with

Fig. 5. Axial and coronal T2-weighted and T1-weighted with or without gadolinium MRI sections of four patients (Patients #10, 11, 12, and 15) treated with everolimus for subependymal giant cell astrocytoma (SEGA). All patients were treated with everolimus due to growing or symptomatic SEGA (left image in each pair of patient images). All patients on follow-up after the indicated number of weeks exhibited marked reduction of SEGA volume (right image in each pair of patient images). All patients experienced a 25% to 50% size reduction after a mean treatment duration of 119 weeks. Arrows indicate the largest SEGA in each patient.
Fig. 6. Four patients who were treated with everolimus due to cardiac rhabdomyoma (RHM) induced obstruction of cardiac outflow or cardiac arrhythmias in neonatal periods. Patient #20 died 3 days after birth and initiation of everolimus due to a rhabdomyoma-induced right ventricle obstruction. In the remaining three patients, initiation of everolimus therapy led to a decrease in rhabdomyoma size and therapeutic control of cardiac arrhythmias. Discontinuation of treatment in the presence of stable disease caused regrowth of the cardiac rhabdomyoma. NA, not available.

<table>
<thead>
<tr>
<th>Patient #</th>
<th>RHM size before treatment (mm)</th>
<th>RHM size after treatment (mm)</th>
<th>Rebound growth after withdrawal (mm)</th>
<th>Duration of treatment (wk)</th>
<th>Starting dose (mg)</th>
<th>Maintenance dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>37.7</td>
<td>19</td>
<td>27</td>
<td>31</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>18</td>
<td>13.5</td>
<td>7.8</td>
<td>11.2</td>
<td>8</td>
<td>0.0625</td>
<td>0.125</td>
</tr>
<tr>
<td>19</td>
<td>16</td>
<td>12.3</td>
<td>15.3</td>
<td>2</td>
<td>0.125</td>
<td>0.25</td>
</tr>
<tr>
<td>20</td>
<td>27</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>0.25</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Fig. 7. Safety profile of oral everolimus. Adverse events developed in 17/20 (85.0%) patients with a median of 3.2 adverse events (range, 0 to 11) per individual. Severe adverse events resulting in discontinuation or dose modification were reported in five patients including drug-induced interstitial lung disease (Patient #1), persistent fever (Patient #3), neutropenia (Patient #17), emotional instability (Patient #16), and oral ulcer (Patient #9). GI, gastrointestinal.
TSC-related multiple manifestations that were successfully treated with everolimus in Korea. Although everolimus was initiated for a single manifestation of a small number of patients, most patients had various manifestations in multiple organs, and we eventually confirmed the integrated efficacy of everolimus treatment on multiple manifestations.

TSC patients showed a wide variety of organ system involvement and severity. TSC-related tumors typically develop in later life, but cardiac RHM is often diagnosed in early life or even prenatally [13]. Because clinical manifestations associated with TSC can be life-threatening, proper monitoring and management are needed to reduce disease-related complications and mortality. Recently published long-term data from EXIST-I and EXIST-II have shown a pronounced and sustained clinical benefit of everolimus [8,10]. It was also confirmed that the number of patients with tumor regression increased over time. The proportion of patients with size reductions of > 50% increased from 45% in 2 years to 62% in 4 years [6,9] in renal AMLs, and the SEGA response rate increased to 58% (95% confidence interval, 47.9 to 67.0) with a median duration of 47.1 months of everolimus treatment [10]. In our study, except for four neonates, 16 adolescent and adult patients (mean age, 32.0 years) were treated with everolimus for mean of 106.9 weeks (range, 30.7 to 289.6) with mean dose intensity of 8.8 mg/day. Tumor regression of > 50% was observed in only 3/14 (21.4%) patients with renal AMLs and no patients with SEGA.

Most patients experienced a 25% to 50% reduction in tumor size. The mean longest diameter of largest AML decreased by 28.8%, and SEGA size decreased by 31.3% on average, which is less responsive than those reported in previous studies [9,10]. This difference in response rate may have resulted from a difference in measurement; this study used the longest diameter rather than the volume of tumors, the patient cohort was small, and the study period was short. In addition, it appears necessary to observe the response rate to everolimus over a long period.

Although it is generally known to exhibit good outcomes and tumor regression, cardiac RHM can be fatal, and immediate intervention may be required in neonatal or young children [14,15]. The U.S. FDA has not approved everolimus for cardiac RHM, yet several studies have observed clinical benefit and safety in using everolimus for the treatment of cardiac RHM in infants and preschool children [12,16,17]. In neonates, even with a small dose for short term (15 days to 13 months), there is a significant size reduction of cardiac RHMs, and everolimus therapy has been well tolerated [16]. In the current study, four neonates with cardiac RHMs that had induced obstruction of cardiac outflow or uncontrolled cardiac arrhythmia were treated with everolimus, and they experienced successful tumor reduction. However, one patient (Patient #18) presented neutropenia as a severe adverse effect of everolimus. Therefore, even with the strong potential of spontaneous regression of cardiac RHM, everolimus should be considered as a therapeutic option for patients at risk of serious cardiac events, including heart failure, outflow obstruction, and arrhythmias.

TSC-related tumors shrink and stabilize with mTOR inhibitor treatment, but after treatment is stopped, tumor volume tends to increase again [18,19]. For this reason, it is often difficult to determine how long a patient should be maintained on a maintenance dose of everolimus to treat TSC-related tumors. In our cohort, three out of 12 patients who were treated with everolimus for more than 1 year for renal AMLs discontinued treatment, and all of them experienced rebound tumor volume increases. Renal AML increased from 7.3 to 8.1 cm (110.0%) over 45 weeks in Patient #1, from 2.6 to 2.9 cm (111.5%) over 54 weeks in Patient #3, and from 2.3 to 3.7 cm (160.9%) over 182 weeks in Patient #4. However, the size of these rebound tumors was the same or smaller than size of the tumor before everolimus treatment was initiated. In cardiac RHM, rebound growth of tumors was also observed in the three patients (Patients #17, #18, and #19) who discontinued everolimus treatment due to a reduction in tumor size, but the tumors of these patients did not exceed the original size and did not cause hemodynamic instability or arrhythmia. This is consistent with previous studies in which renal AML or cardiac RHM rebound growth occurred following withdrawal of mTOR inhibitors [12,19,20]. The regrowth of tumors after the cessation of an mTOR inhibitor suggests that continued treatment with everolimus in TSC patients may be required to sustain significant tumor volume reduction. Alternatively, if problems emerge during treatment, such as severe adverse effects, short-term mTOR inhibitor use during the critical period followed by tumor monitoring can be performed. Therefore, it is necessary to study the proper timing of dose reduction or discontinuation while administering mTOR inhibitors in TSC patients.

Because TSC is a lifelong disease that begins at a very early age, it is important to consider the long-term effects of mTOR inhibitors on overall safety and growth in young children [21]. A cohort analysis of mTOR inhibitor treatment in children who received renal transplants reported that approximately 5 years of mTOR treatment had no significant impact on growth and pubertal development [22]. However, large-scale studies of the long-term effects and safety of mTOR inhibitor administration in patients with TSC over 10 or 20 years is still required.

In this study, adverse events were reported in 17 cases (85.0%) in the order of mucositis, dyslipidemia, hypertension, headache, gastrointestinal troubles, and worsening of acne or folliculitis. In order to prevent oral mucositis, patients were instructed to swallow...
the drug as soon as possible, and edible-wrapping papers was recommended to use. Serious adverse events including drug-induced interstitial lung disease, persistent fever, neutropenia, emotional instability, and severe oral ulcer resulted in discontinuation or dose modification in five patients. However, these events were reversible, returning to normal when the drug was reduced or dropped.

In this retrospective study, despite the small patient cohort, the data show a significant treatment response to everolimus in patients with TSC-associated epilepsy and cardiac RHM in addition to renal AML and SEGA. Further long-term studies with larger patient cohorts will be required to confirm the effectiveness, safety, timing, and duration of everolimus treatment in TSC patients.

In conclusion, everolimus, an mTOR inhibitor, can be effective for multiple clinical manifestations of TSC patients. However, clinicians should also be aware of the adverse events profile of everolimus and continue to study the long-term efficacy and frequency of side effects in the future.

**Conflicts of interest**

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

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Conceptualization: HA, MSY, and TSK. Data curation: HA, MSY, and HNJ. Formal analysis: HA and MSY. Methodology: HA and MSY. Project administration: HA and MSY. Visualization: HA and MSY. Writing-original draft: HA. Writing-review & editing: MSY, CS, and TSK.

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**References**


Bilateral Tonic Pupils and Guillain–Barre Syndrome in a 6-Year-Old Boy

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Bilateral tonic pupils can be a rare manifestation of Guillain-Barré syndrome (GBS). Here we report our experience of bilateral tonic pupils in a child with GBS, who diagnosed by pharmacological pupil test with diluted 0.125% pilocarpine and nerve conduction velocity (NCV) study.

A 6-year-old boy was transferred to our hospital due to altered mental status after respiratory resuscitation. One day before the transfer, he had gastrointestinal symptoms and weakness for dehydration. Few hours before the transfer, he abruptly started vomiting and developed difficulty in breathing. Upon arrival at the emergency room, he was intubated and mental status was stupor (Glasgow coma scale E2V2M5, temperature 37.7°C, blood pressure 110/65 mm Hg, respiratory rate 25/min). Both pupils were dilated > 5 mm and light reflexes were hardly detected bilaterally. He was flaccid and deep tendon reflexes were decreased.

He was born at full term by uncomplicated delivery (birth weight 4,000 g). Before admission, he had been healthy and neurodevelopment was normal. Medical and family histories were unremarkable. He had not been vaccinated recently. The initial laboratory results for blood, stool, and cerebrospinal fluid (CSF) were unremarkable, except for a mild hyponatremia (Table 1). Chest radiographs revealed right upper lobe atelectasis and peribronchial infiltrations, indicating aspiration pneumonia. Brain diffusion magnetic resonance imaging (MRI) at the emergency room and regular brain and spinal MRI scans on the fifth day showed no brain or spinal cord injury. There was no enhancement or thickening of upper and lower cranial nerves on brain MRI. Electroencephalography revealed diffuse cerebral dysfunction on the first day. Due to possibility of encephalopathy, hypoxic injury, or severe pneumonia, intravenous (IV) antibiotics and IV acyclovir were started, and the respiratory function and intracranial pressure increase signs were carefully monitored. Additionally, considering the possibility of rapidly aggravating GBS, we initiated intravenous immunoglobulin (IVIG) treatment from the second day (400 mg/kg/day for 5 days).

Within a few days, the patient became alert and his respiratory functions improved. However, the generalized motor weakness and pupil dilatation persisted. Ptosis or anhidrosis was not noted. The weakness was more severe in the lower (grade 2) than in the upper extremities (grade 3). On the 5th day, he was extubated. The pupil dilatation slowly improved to 5 mm, but the light reflex was weak and present only in the

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right eye. Ocular movements were normal; he could watch movies on his smartphone and track moving objects. We performed a pharmacological test on the pupils using diluted 0.125% pilocarpine drops. By dropping the pilocarpine for an hour, pupillary constriction was induced, which was not observed in normal condition (Fig. 1). This finding corresponded to bilateral tonic pupils.

The patient’s motor functions gradually recovered from upper to lower limbs, and pupil size and reflexes normalized. Rehabilitation consultation was performed and physiotherapy was started. On the 16th day, he could walk without assistance. NCV study was performed on the 16th day, and the results showed F-wave absence, reduced conduction velocity by demyelination, or reduced compound action potential amplitude in the axonal forms [1]. This finding suggested ascending paralysis [3]. However, no improvement was observed in compound muscle action potential amplitude [1], which was consistent with the findings of the clinical manifestation and laboratory findings, we finally diagnosed him as rapidly developed GBS with respiratory muscle involvement and some are intubated at the peak of illness. Autoimmunity or NCV may reveal pathological changes—F response absence, reduced conduction velocity by demyelination, or reduced compound action potential amplitude in the axonal forms [1].

In case of suspicion of GBS, children should be hospitalized until stabilization. IVIG should be started as soon as possible. After 2 weeks of a plateau period, most patients gradually recover with patterns inverse to those of the progression. However, younger age and rapid progression may be correlated with long-term compromises [1]. Rare severe fulminant GBS manifested as locked-in syndromes reported in an infant with herpes simplex virus infection [2].

In the present case, the patient initially thought as flaccid paralysis with aspiration pneumonia of unknown etiology. During the treatment, his mentality recovered soon. His clinical feature improved significantly with IVIG, and he recovered as descending pattern. The NCV test result at subacute stage and bilateral tonic pupil further supported the diagnosis of a form of GBS [3,4].

### Table 1. Laboratory results of the patient

<table>
<thead>
<tr>
<th>Blood analysis at arrival</th>
<th>CSF examination</th>
<th>Others</th>
</tr>
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<tbody>
<tr>
<td>Arterial blood gas (with O₂); pH 7.42, pO₂ 189.5 mm Hg, pCO₂ 35.8 mm Hg, HCO₃⁻ 23.5 mmol/L, SaO₂ 99.7%, WBC 3,700/μL, Hb 12.1 g/dL, platelets 301 K/μL, sodium 129 mEq/L, potassium 4.3 mEq/L, calcium 9.2 mg/dL, glucose 95 mg/dL, ALT/AST 12/27 IU/L, CK 67 IU/L, lactate 0.9 mmol/L, ammonia 56 μmol/L</td>
<td>Opening pressure 12 mm H₂O, WBC 1/mm³, RBC 1/mm³, protein 27 mg/dL, glucose 61 mg/dL, chloride 125 mg/dL, CSF PCRs for enterovirus (-), HSV (-), and mycoplasma (-), bacterial culture (-), IgG index 0.029 (ref &lt; 0.7)</td>
<td>Serum HSV IgG/IgM (+/-), CMV IgG/IgM (+/-), EBV IgG/IgM (+/-), mycoplasma IgG/IgM (+/-), GM1 IgG/IgM (-/-), GD1b IgG/IgM (-/-), and GQ1b IgG/IgM (-/-); throat PCR for enterovirus (-); stool PCR for C jejuni (-); nasopharyngeal PCR for respiratory viruses (-)</td>
</tr>
</tbody>
</table>

WBC, white blood cell; Hb, hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatinine kinase; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; HSV, herpes simplex virus; IgG, immunoglobulin G; IgM, immunoglobulin M; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GM1, monosialotetrahexosylganglioside 1; GD1b, disialosyl gangliosides 1b; GQ1b, quadrisialosyl gangliosides 1b; C. jejuni, Campylobacter jejuni.

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**Fig. 1.** (A) Before 0.125% pilocarpine administration; fixed and dilated pupils, irresponsible to light. Ocular movements were normal. (B) An hour after 0.125% pilocarpine administration; pupillary constriction which does not occur in normal conditions.

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Bilateral tonic pupils are caused by abnormalities of the ciliary ganglion or a postganglionic parasympathetic branch of the ciliary nerve [3,4]. In adults, bilateral tonic pupils are frequently idiopathic. Generalized peripheral neuropathy, autonomic neuropathies, diabetes mellitus, paraneoplastic syndromes, and other generalized diseases can manifest bilateral tonic pupils [4]. In GBS, demyelination of the postganglionic ciliary nerve can be manifested as tonic pupils. It may occur without extraocular muscle paralysis [4]. However, this condition is rare in adults and extremely rare in children [2,3,5]. The youngest child reported was an 11-year-old boy [5]. Diagnosis is based on instillation of diluted pilocarpine (0.0625% to 0.125%); it causes a supersensitive pupillary constriction in GBS, which does not appear in normal conditions [3,4]. In the present letter, we report a very rare case of acute bilateral tonic pupils in a child with GBS. Postganglionic involvement of the parasympathetic nerves may be the underlying cause. The pharmacological pupil test with diluted 0.125% pilocarpine was helpful for the diagnosis.

Written informed consent was obtained from parent. This study was approved by the Institutional Review Board at Hanyang University Guri Hospital (2019-07-023-002).

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

References

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Novel Mutation in KCNQ2 Causing Ohtahara Syndrome

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Ohtahara syndrome is rare and the earliest-appearing age-related epileptic encephalopathy. It is also known as early infantile epileptic encephalopathy with burst-suppression [1]. Seizures onset occurs during the first 3 months of life, often in the form of frequent tonic spasms and partial seizures within the first 2 weeks. We report the first case of Ohtahara syndrome with a novel missense mutation of potassium voltage-gated channel subfamily Q member 2 (KCNQ2) gene (p.Arg207Pro) in Korea that was partially responding to ketogenic diet.

Our patient was born at 38 weeks, 2 days gestation after an uncomplicated pregnancy. Her birth weight was 3.2 kg, and Apgar score was 8/9. She had uncontrollable seizures from the 2nd day after birth. Seizures were tonic in nature involving both the upper limbs and lower limbs, with left deviation of the eyes and cyanosis. Multiple attacks were encountered per day, and each episode took approximately 1 minute. General and neurologic examinations were unremarkable except mild head lagging. Laboratory investigations including electrolyte, congenital infection and test of inborn error of metabolism showed no significant findings. First electroencephalography (EEG), done 6 days after birth, showed hypsarrhythmia and burst-suppression pattern. First magnetic resonance imaging of the brain done on the same day was normal.

Although multiple antiepileptic drugs were given, brief tonic or myoclonic seizures continued about 10 times a day. Also, her development was constantly delayed. At 6 months of age, her EEG revealed hypsarrhythmia with chaotic background and multifocal sharp waves (Fig. 1). Steroid pulse therapy was not effective. She was therefore put on ketogenic diet at 6 months of age using a ketogenic formula (Ketonia, Namyang Co. Ltd, Seoul, Korea). After a few days of complete ketogenic diet, her seizures were reduced to one or two times a day. Her ketogenic diet continued for 24 months and then gradually stop.

Her genetic test with next generation sequencing revealed a missense mutation in KCNQ2 gene (c.620G > C [p.Arg207Pro]) and were likely pathogenic by American College of Medical Genetics and Genomics guideline 2015, that were not previously reported (Fig. 2). KCNQ2 gene test for her parents showed negative result. Therefore, she was identified as Ohtahara syndrome due to de novo mutation of KCNQ2 gene. Currently, she had brief tonic or myoclonic seizures about less than once a day and bed-ridden state.

Among KCNQ2 related epilepsy, Ohtahara syndrome is the most critical finding for discrimination [2]. Sodium channel blockers like phenytoin and carbamazepine have been reported to be effective in the treatment of KCNQ2-related epilepsy [3]. In this patient, we used phenytoin and topamax but both were not effective.
Fig. 1. Electroencephalography at 6-month age revealed hypsarrhythmia with chaotic background and multiple sharp waves.
at all and seizure was partially controlled by ketogenic diet. Ketogenic diet, mechanistic target of rapamycin inhibitors, is an effective targeted treatment for KCNQ2 encephalopathy, respectively. The patient showed partial response to the ketogenic diet at 6-month-old, but the seizure was not fully controlled and she is currently on a bed-ridden state. Therefore, early and active genetic testing for precision medication is important in patients with suspected Ohtahara syndrome.

**Conflicts of interest**

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

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**References**


**Fig. 2.** Genetic analysis of the patient revealed a novel potassium voltage-gated channel subfamily Q member 2 (KCNQ2) missense mutation (c.620G>C [p.Arg207Pro]).
A Novel Pathogenic Variant (c.592_599del) in PCDH19 in a Korean Family with Epilepsy

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Protocadherin 19 (PCDH19)-related epilepsy is an X-linked epilepsy syndrome characterized by afebrile or febrile seizures, starting in the early years of life, and developmental delay of variable severity [1]. It is caused by mutations in PCDH19 encoding PCDH19, a protein highly expressed during brain development, that is responsible for calcium-dependent cell-to-cell interaction. The disease is of very characteristic heredity; although it is an X chromosome linked disorder, it rarely affects male individuals; this is attributed to "cellular interference," where the disease could be caused by cell-to-cell signaling between mutated and unmutated cells resulting in hemizygous men being unaffected. Here, we report the case of two Korean female siblings, in which a novel pathogenic variant of PCDH19, inherited from the father, caused different phenotypic expression.

A 23-month-old girl (Sibling 1, III:3) began experiencing generalized tonic clonic seizures lasting 3 to 5 minutes and brief unilateral tonic seizures lasting approximately 1 minute. Unresponsiveness with eye blinking lasting less than 1 minute was also detected. Her brain magnetic resonance imaging was normal, and there was no evidence of central nervous system infection in her cerebrospinal fluid study. She was neurologically intact without deficits and remained alert during the interictal periods, with no more seizures detected after levetiracetam infusion (30 mg/kg). We were informed that she had relevant family history; her 10-year-old sister had epilepsy and her mother had febrile seizures at an early age (Fig. 1). Her sister (Sibling 2, III:2) started experiencing febrile seizures at 13 months of age and had clustered brief seizures with or without fever similar to Sibling 1. Administration of multiple antiepileptic drugs was attempted for several years and the frequency of seizures decreased with age. In recent years, she had remained seizure free with levetiracetam monotherapy and her intelligence and social function were within the normal range, but her language skills were relatively delayed. Her mother had febrile seizures at an early age, which dissipated at 3 years of age and her intelligence was within the
The multitude of genes associated with epilepsy and the similarity among clinical phenotypes may complicate diagnosis; hence, we performed whole exome sequencing (WES) with the informed consent of the family members (II:1, II:2, III:2, and III:3). Family-based WES is a very powerful tool for identifying pathogenic variants using expected inheritance patterns.

After screening of epilepsy-related genes, we identified a novel deletion variant (NM_001184880.1:c.592_599del) in PCDH19, which was predicted to result in frameshift and premature termination of the PCDH1 protein (p.Arg198Alafs*25) (Fig. 2). The variant was identified as a heterozygote in the two siblings (III:2 and III:3) and as a hemizygote in the father (II:1), but not in the mother (II:2). No other strong candidate genes were located in the WES results. Sibling 1 has remained seizure free for over 6 months with levetiracetam monotherapy (30 mg/kg/day) and has so far normally reached the developmental milestones.

Seizures usually start before 1 year of age, and the presence of fever-sensitive seizures may be clinically similar to the presentation of Dravet syndrome, but seizures in Dravet syndrome usually last longer than 15 minutes (72% of patients) and less than 5 minutes in PCDH19-related epilepsy [1]. Dravet syndrome usually involves clonic or hemiclonic-type seizures, whereas PCDH19-related epilepsy usually involves the focal or hypomotor type. Most importantly, there is a significant difference in prognosis, with remission in adolescence with variable severity of developmental delay being common in PCDH19-related epilepsy, as in our case and severe epileptic encephalopathy often seen in Dravet syndrome [2]. Regarding anticonvulsant treatment, phenytoin is re-

**Fig. 1.** Pedigree of the family, with two related cases of PCDH19-related infantile epileptic encephalopathy. A pathogenic PCDH19 variant, c.592_599del is found hemizygous in the father (II:1) and heterozygous in the two siblings (III:2 and III:3). The mother (II:2) is homozygous for the wild-type (WT) allele. The black symbols indicate the affected individuals.

**Fig. 2.** Molecular analyses of PCDH19 in two siblings with epilepsy. (A) Integrative Genomics Viewer (Broad Institute and the Regents of the University of California) snapshot of a novel PCDH19 deletion variant identified by whole exome sequencing (arrow). (B) Frameshift and premature termination of the PCDH1 protein (p.Arg198Alafs*25).
portedly effective and carbamazepine less so [3]. There have been reports of effective levetiracetam use, including in these siblings, which should be studied further [4]. Fever-sensitive seizures and prominent seizure clustering in varied patterns with short duration (< 5 minutes) in girls younger than 1 year, as in our cases, can provide clues for PCDH19-related epilepsy to clinicians [1,4,5].

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.26815/acn.2019.00199.

Conflicts of interest

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References

Instructions to authors

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4) Tables should be concise and not duplicate information found in figures.
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