Aims and scope

Annals of Child Neurology is an interdisciplinary peer-reviewed biomedical journal publishing articles in the fields of child neurology, pediatric neurosurgery, pediatric neuroradiology, child psychiatry, pediatric neuropsychology, developmental and behavioral 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, sleep medicine, vascular neurology, as well as other diseases affecting the developing nervous system.

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

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The Wide Variety of Acute Disseminated Encephalomyelitis in Children: A Clinical Perspective

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Acute disseminated encephalomyelitis (ADEM) is an acute demyelinating inflammatory disorder of the central nervous system. It is characterized by encephalopathy, multifocal neurological deficits, and typical magnetic resonance imaging findings of widespread demyelinating lesions, predominantly involving the white matter of the brain and spinal cord. ADEM mainly affects children and is commonly associated with preceding viral and bacterial infections, and, rarely, vaccinations. Despite substantial advances in the understanding of the association of myelin oligodendrocyte glycoprotein antibody with recurrent forms of ADEM or other demyelinating conditions, specific etiologic agents or biological markers have not been identified. Therefore, the diagnosis of ADEM is still based on clinical and radiological findings and the exclusion of other conditions mimicking ADEM. However, a prompt diagnosis and adequate treatment are crucial because diagnostic delays or inappropriate treatment may lead to unwanted neurological sequelae in some children. There is no standardized treatment protocol for ADEM, but the use of corticosteroids, intravenous immunoglobulin, and plasmapheresis has been associated with good clinical outcomes. Adequate treatment has reportedly resulted in favorable outcomes, with full or almost full recovery in most children with ADEM, although some children may develop neurological sequelae, such as cognitive impairment and motor deficits. Further studies are needed to identify biological clues and optimal treatment protocols to minimize the incidence of neurological sequelae.

Keywords: Encephalomyelitis, acute disseminated; Acquired demyelination syndrome; Myelin oligodendrocyte glycoprotein antibody

Introduction

Acute disseminated encephalomyelitis (ADEM) is an acute or subacute immune-mediated demyelinating inflammatory disorder of the central nervous system (CNS). It is characterized by encephalopathy with multifocal neurological deficits and characteristic magnetic resonance imaging (MRI) findings of widespread demyelination, predominantly involving the white matter of the brain and spinal cord, and mostly occurs after recent viral or bacterial infections [1-4]. It is predominantly diagnosed in children, is usually monophasic, and often resolves within 3 months of treatment. The International Pediatric Multiple Sclerosis Society Group (IPMS-
SG) made enormous efforts to create consensus clinical and radiological diagnostic criteria for ADEM in 2013 (Table 1) [5]. In addition, the discovery of myelin oligodendrocyte glycoprotein antibody (MOG-Ab) and understanding of its association with recurrent forms of ADEM, such as multiphasic ADEM (MDEM), have made its diagnosis and management possible [6-8]. Despite these advances, the diagnosis is still made based on clinical and MRI findings, and minimal modifications have been made in the treatment protocol over these years. Although the overall prognosis is usually favorable, some patients with ADEM might develop neurological sequelae such as cognitive impairment, motor deficits, visual problems, and epilepsy [9-11]. Relapse can occur in a minority of children with ADEM, although there are gray zones between relapsing ADEM and other neuroinflammatory demyelinating conditions, such as neuromyelitis optica spectrum disorder (NMOSD) and MOG-Ab-associated disorders (MOGAD). This review focuses on the current knowledge and recent advances in the management of pediatric ADEM.

**Epidemiology**

ADEM can occur at any age, but predominantly develops in childhood and adolescence. Its annual incidence is estimated to be 0.3 to 0.6 cases per 100,000 children with a mean age of 5 to 8 years at presentation [2,4,12]. Previous studies have reported a slight male preponderance, with male-to-female ratios ranging from 1:0.8 to 2.3:1 [13]. Its incidence is highest in winter and spring [12]. It is also more common with increasing distance from the equator, similar to multiple sclerosis (MS) [2]. ADEM is now considered a form of autoimmune encephalitis. It often occurs after infection or, rarely, after vaccination. In 50% to 86% of cases, ADEM is reportedly preceded by an acute infectious illness such as upper respiratory infections, gastroenteritis, and rarely an exanthematous disease due to various agents [1,4,12,14]. Clinical symptoms typically begin within 2 days to 3 weeks after an infectious event [12]. The most frequent associated infections are viral infections, but bacteria or other agents have also been implicated (Table 1) [2,12,14-19]. Pediatric ADEM cases after infection with severe acute respiratory syndrome coronavirus 2 have also been reported [20,21]. Vaccinations have been implicated as a triggering factor for ADEM in 4% to 18% of cases [1]. Almost all vaccines have been implicated; however, no clear causal association has been proven (Table 1). Reportedly, the first vaccination is more likely to trigger ADEM than subsequent vaccinations [22].

**Pathogenesis**

The pathogenesis of ADEM remains unclear, but may involve an immune-mediated inflammatory process triggered by infection or vaccination in genetically predisposed individuals. Previous studies have proposed that some children with certain human leukocyte antigen subtypes are more likely to develop ADEM [23-25]. Molecular mimicry between antigenic determinants of neurotropic viruses or other causative agents and myelin agents such as myelin basic protein (MBP) and MOG is considered a putative mechanism underlying immune-mediated neuronal injury [2,26,27]. Another theory is non-specific self-sensitization of reactive T cells (bystander activation) against myelin proteins resulting from infectious antigens [28]. This reactivation makes it possible for T cells to migrate through glial limitans and enter the brain parenchyma. The production of cytokines and chemokines by antigen-presenting cells and activated T cells contributes to further recruitment, which boosts migration into the CNS of additional immune cells, such as T cells and macrophages. Breakdown of the blood-brain barrier is also caused by the release of proteases from activated T cells, mast cells, and monocytes. Furthermore, T cells possibly play a secondary role in other inflammatory processes that can cause demyelination and axonal injury [29]. The autoimmune hypothesis is also supported by the fact that anti-MOG-Abs have been identified in both serum and cerebrospinal fluid (CSF) during the

### Table 1. Causative agents of acute disseminated encephalomyelitis

<table>
<thead>
<tr>
<th>Infections</th>
<th>Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria:</strong> Borrelia burgdorferi, Campylobacter jejuni, Chlamydia pneumoniae, Haemophilus influenzae type b, Leptospira, Legionella pneumoniae, Mycoplasma pneumoniae, Rickettsia, beta-hemolytic Streptococcus</td>
<td>Diphtheria/pertussis/tetanus, hepatitis B, influenza, Japanese B encephalitis, measles, mumps, rubella, pneumococcus, polio, rabies, SARS-CoV-2, smallpox, varicella</td>
</tr>
<tr>
<td><strong>Viruses:</strong> Coronavirus/SARS-CoV-2, Coxsackie virus, CMV, EBV, dengue virus, hepatitis A virus, HHV-6, HIV, HSV, influenza virus, Japanese encephalitis virus, measles virus, rubella virus, varicella zoster virus, West Nile virus, Zika virus</td>
<td></td>
</tr>
<tr>
<td><strong>Others:</strong> Toxoplasma gondii, Plasmodium falciparum, Cryptococcus neoformans</td>
<td></td>
</tr>
</tbody>
</table>

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV-6, human herpesvirus 6; HIV, human immunodeficiency virus; HSV, herpes simplex virus.
acute phase in 36% to 60% of children with ADEM, which progressively declines during the recovery phase [30,31]. High and persistent MOG-immunoglobulin G titers are usually associated with relapsing forms of MOGAD [31-33]. However, it remains uncertain whether anti-MOG-Abs are causative agents or byproducts of extensive myelin degradation in ADEM or other demyelinating diseases.

Clinical/diagnostic perspectives

1. Clinical features
The initial symptoms typically begin within 2 days to 3 weeks of infection or vaccination. The clinical presentation is diverse; however, patients with ADEM typically show non-specific prodromal symptoms, such as fever, malaise, headache, nausea, and vomiting shortly before neurological symptoms or signs. The clinical course is characterized by rapid progression and development of maximum deficits within a few days [12]. Neurological manifestations typically begin with encephalopathy, characterized by altered consciousness, such as irritability, lethargy, coma, and abnormal behavior, which are associated with focal or multifocal neurological deficits depending on the lesions. In addition, they can present with masquerading symptoms or signs, such as fever, seizures, and meningeal irritation, resembling meningoencephalitis. ADEM can affect any part of the brain, spinal cord, or peripheral nerves, meaning that it can present with any type of neurological symptoms. Common neurological symptoms include pyramidal signs, cranial neuropathy, speech impairment or aphasia, sensory deficits, visual disturbances, ataxia, and spinal cord signs (Table 2). Children with anti-MOG-Abs tend to have multifocal neurological symptoms but show complete resolution after steroid treatment [4]. Pediatric intensive care unit (PICU) admission is required in 15% to 25% of children with ADEM, mainly due to respiratory failure, which results from coma, brainstem involvement, and status epilepticus [1,6,34]. Combined central and peripheral demyelination is also common in children. However, a further diagnostic work-up can be performed to screen for other conditions, such as metachromatic leukodystrophy and Krabbe disease in certain cases. ADEM is typically a monophasic condition but can show a relapsing form described as “recurrent” if the lesions are always the same, or “multiphasic” if the space and time of the lesions are widely dispersed. This relapsing form, such as MDEM, appears to be related to high and persistent MOG-Ab titers [4,31,32].

2. Neuroimaging features
Because there are no specific biomarkers for diagnosis, MRI is still the most sensitive technique for diagnosing ADEM. Brain MRI in the acute phase typically shows diffuse, bilateral, randomly distributed, large (1 to 2 cm), patchy or tumor-like, often heterogeneous, poorly demarcated hyperintense lesions on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences [12,26]. Both white and gray matter are affected. When the deep gray matter is affected, it is more likely to be symmetrical and often involves the thalami and basal ganglia. Apart from these lesions, other patterns have been reported in pediatric ADEM (Table 3) [1,12,35]. Fig. 1 demonstrates various patterns of MRI lesions in pediatric patients with ADEM. Brain MRI may show subtle or no abnormalities in the early phase of ADEM. This type of delay should be taken into consideration if the case is clinically suggestive of ADEM, but the initial MRIs do not show any abnormal findings [36,37]. Spinal cord involvement has been reported in 18% to 80% of children with ADEM, and longitudinally extensive transverse myelitis (LETM) involving at least three vertebral body segments in length has been detected in 60% to 100% of patients [1]. Children with anti-MOG-Ab positive ADEM are at a higher risk of LETM [32]. Gadolinium enhancement is reported in 18% to 50% of patients.

### Table 2. Clinical/neurological features of acute disseminated encephalomyelitis

| Encephalopathy: sleepiness/irritability to coma |
| Fever                                      |
| Headache                                   |
| Seizures                                   |
| Meningeal irritation signs                  |
| Cranial neuropathy                         |
| Pyramidal signs, unilateral or bilateral    |
| Ataxia                                     |
| Optic neuritis                             |
| Bladder insufficiency                      |
| Sensory deficits, unilateral or bilateral   |

### Table 3. Various magnetic resonance imaging patterns of acute disseminated encephalomyelitis

- Diffuse, bilateral, large, confluent, tumor-like lesions with perilesional edema
- Bilateral, small isolated subcortical white matter lesions
- Periventricular white matter lesions
- Cortical gray matter lesions
- Cerebral white matter lesions with bilateral thalamic or basal ganglia involvement
- Cerebral white matter lesions with cerebellum, brainstem, or spinal cord involvement
- Diffuse, bilateral, symmetrical leukodystrophy-like white matter lesions
- Black holes/T1 hypointensities
- Hemorrhagic pattern within the large, confluent white matter lesions
There have been conflicting results regarding MRI diffusion patterns. However, no restricted diffusion on diffusion-weighted imaging and apparent diffusion coefficient map with high values consistent with vasogenic edema were found in 75% of patients [1]. Verifying the resolution of lesions in serial MRI studies can play a crucial role in bolstering the initial diagnosis of ADEM.

### 3. Laboratory findings

There are no laboratory tests specific to ADEM. Many tests are useful in ruling out other neurological conditions. CSF findings are usually non-specific, including mild pleocytosis with lymphocyte predominance and slightly elevated protein levels. Oligoclonal bands, the only established biomarker of MS, are detected in 0% to 20% of patients with ADEM [1]. Although there are no specific biomarkers for ADEM, serum anti-MOG-Ab and anti-aquaporin 4 antibody (anti-AQP4-Ab) tests are useful in certain cases. Anti-MOG-Ab was detected in approximately 33% to 66% of pediatric ADEM cases and 96% of ADEM cases that developed a relapsing form of demyelination [1]. Anti-AQp4-Ab tests are useful in ruling out other neurological conditions. CSF findings are usually non-specific, including mild pleocytosis with lymphocyte predominance and slightly elevated protein levels. Oligoclonal bands, the only established biomarker of MS, are detected in 0% to 20% of patients with ADEM [1]. Although there are no specific biomarkers for ADEM, serum anti-MOG-Ab and anti-aquaporin 4 antibody (anti-AQP4-Ab) tests are useful in certain cases. Anti-MOG-Ab was detected in approximately 33% to 66% of pediatric ADEM cases and 96% of ADEM cases that developed a relapsing form of demyelination [1]. Anti-AQP4-Ab tests are specific for NMOSD, a major type of ADEM that mimics demyelinating disorders. A case-control study showed 91% sensitivity and 100% specificity for anti-AQP4-Ab in NMOSD [38].

### 4. Electroencephalography

Electroencephalography (EEG) is often performed in pediatric ADEM because of seizures or altered consciousness at presentation. The most common abnormal finding is non-specific, diffuse slowing in 80% to 88% of patients [39-41]. Focal epileptiform discharges are identified in 15% to 25% of patients [39-41]. It seems that there are no significant associations between EEG findings and clinical features, or between abnormal EEG findings and epilepsy development [1].

### 5. ADEM subtypes

Based on the relapse and time course of ADEM, the IPMSSG has proposed an operational definition for ADEM and its variants [5]. Although debated, ADEM subtypes include ADEM, MDEM, ADEM-optic neuritis (ADEM-ON), and exceptionally acute hemorrhagic encephalomyelitis (AHEM) (Table 4). Monophasic ADEM refers to a single ADEM episode with no further demyelinating events or new MRI findings. If a relapse occurs within the first 3 months of the initial episode, it is still considered the same episode. MDEM indicates two or more episodes of ADEM separated by at least 3 months. ADEM-ON is monophasic or MDEM with one or more recurrent episodes of optic neuritis. AHEM is a severe, fatal form of ADEM with rapid deterioration and poor outcomes, and it is associated with multifocal hemorrhages and necrosis in addition to typical demyelinating lesions. Death can occur within 24 hours of onset due to severe brain edema or herniation. These diagnoses are not final because ADEM is a heterogeneous entity that can evolve into other types. As a result, it must be considered whether patients develop additional attacks or unusual presentations that are remote from the initial episode.

### 6. Diagnosis

The diagnosis is still based on clinical and radiological findings and the exclusion of other conditions mimicking ADEM because there are no specific biomarkers for confirmation. The IPMSSG proposed updated diagnostic criteria for ADEM in 2013, even though the criteria are still limited in certain cases (Table 5) [5]. Taking a
The diagnosis of ADEM is mainly based on clinical and radiological findings. As a result, diagnosis often requires the exclusion of a wide variety of ADEM-mimicking conditions. Many acquired demyelination diseases and other inflammatory or non-inflammatory conditions may show similar clinical and radiological features and should be considered in terms of the differential diagnosis (Table 6).

First, potentially treatable viral or bacterial CNS infections should be ruled out. When a patient presents with movement disorders, seizures, altered consciousness, or other neuropsychiatric symptoms a few days to weeks after an infection or vaccination, autoimmune encephalitis such as anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis should be considered. Besides other immune-mediated demyelinating disorders, stroke-like episodes potentially indicate CNS vasculitis, systemic lupus erythematosus, moyamoya disease/syndrome, or rarely, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes. Bilateral thalamic involvement may be observed in children with ADEM, but it can also be noted in children with acute necrotizing encephalopathy or deep cerebral venous infarction. Bilateral basal ganglia involvement can be observed in toxic, metabolic, or genetic disorders. Bilateral cortical and subcortical lesions, predominantly in the parieto-occipital lobes, are indicative of posterior reversible encephalopathy syndrome, especially in children who are exposed to hypertension or immunosuppressive agents. If the clinical course progressively worsens, CNS tumors or genetic disorders should be considered.

Table 4. Subtypes of ADEM

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monophasic ADEM</td>
<td>A single ADEM episode with no further demyelinating events or new MRI lesions</td>
</tr>
<tr>
<td>Multiphasic ADEM</td>
<td>Two episodes of ADEM separated by at least 3 months in time</td>
</tr>
<tr>
<td>ADEM-ON</td>
<td>Monophasic or multiphasic ADEM plus one or more recurrent episodes of optic neuritis</td>
</tr>
<tr>
<td>AHL/AHEM</td>
<td>A severe fulminating form of ADEM with rapid deterioration and poor outcomes; associated with multifocal hemorrhages and necrosis in addition to typical demyelinating lesions</td>
</tr>
</tbody>
</table>

ADEM, acute disseminated encephalomyelitis; MRI, magnetic resonance imaging; ADEM-ON, ADEM-optic neuritis; AHL, acute hemorrhagic leukoencephalitis; AHEM, acute hemorrhagic encephalomyelitis.

The second attack at least 3 months after the initial attack, along with new lesions or three or more attacks, suggests the ultimate diagnosis of multiple sclerosis, neuromyelitis optica, or other disorders. No other demyelinating attacks occur. Monophasic ADEM is followed by recurrent optic neuritis in the vast majority of cases, which seems to be associated with myelin oligodendrocyte glycoprotein.

Table 5. Diagnostic criteria for ADEM

1. A first polyfocal, clinical, CNS event with presumed inflammatory demyelinating cause
2. Encephalopathy not explained by fever, systemic illness, or postictal symptoms
3. Brain MRI is abnormal during the acute (3 months) phase
4. No new clinical or MRI findings emerge 3 months or more after onset
5. Brain MRI is abnormal during acute (3 months) phase with diffuse, poorly demarcated, large (1–2 cm) lesions involving predominantly cerebral WM. T1 hypointense lesions in WM are rare. Deep GM lesions in the thalamus or basal ganglia can be present

Adapted from the International Pediatric Multiple Sclerosis Society Group (IPMSSG) Diagnostic Criteria for ADEM, 2013.

ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; MRI, magnetic resonance imaging; WM, white matter; GM, gray matter.
Table 6. Differential diagnosis of acute disseminated encephalomyelitis

- Meningoencephalitis/encephalitis: viral (HSV, EBV, CMV, HIV), bacterial, parasitic
- Immune: autoimmune encephalitis (anti-NMDAR-Ab)
- Inflammatory demyelinating: MS, NMO
- Vascular/vasculitis: moyamoya disease, SLE, etc.
- Toxic/metabolic/hypoxic/radiation induced
- Neoplastic: multicentric glioma, glioblastoma multiforme, CNS lymphoma, histiocytosis
- Others: PRES, MELAS, ANE, etc.

HSV, herpes simplex virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; HIV, human immunodeficiency virus; anti-NMDAR-Ab, anti-N-methyl-D-aspartate receptor antibody; MS, multiple sclerosis; NMO, neuromyelitis optica; SLE, systemic lupus erythematosus; CNS, central nervous system; PRES, posterior reversible encephalopathy syndrome; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome; ANE, acute necrotizing encephalopathy.

Treatment

Since there are no randomized placebo-controlled studies on the treatment of ADEM, treatment protocols are mainly based on expert opinions and observational studies. Symptom-based supportive care is important because of its onset at any age or stage of illness. Supportive care can be provided together with curative treatment. Treatment with antiviral agents and antibiotics is generally accepted because ADEM mimics CNS infection.

The standard protocol is a non-specific immunosuppressive therapy including corticosteroids, intravenous immunoglobulins (IVIGs), plasma exchange (PE), and other immunomodulatory agents. Despite the lack of convincing evidence, first-line treatment usually involves a short course of high-dose corticosteroids. The most widely used protocol consists of methylprednisolone administered at 10 to 30 mg/kg/day to a maximum dose of 1 g/day or dexamethasone administered at 1 mg/kg/day, followed by oral prednisone at 1 mg/kg/day and tapered over 4 to 6 weeks [12,43,44]. In cases where corticosteroids yield poor results, IVIGs can be administered as an alternative treatment, which is administered at a total dose of 2 g/kg administered either as a single dose or divided doses over 2 to 5 days [1,12,45]. Another alternative is PE, which is usually used in children who fail to respond to corticosteroids or IVIGs (Fig. 2). PE usually involves 3 to 6 cycles with widely different protocols, and the clinical response is usually obvious after 2 to 3 exchanges [46,47].

Cyclophosphamide can be used in patients in whom conventional treatment fails, and other disease-modifying drugs such as
azathioprine, mycophenolate, and rituximab can be favorable in children with recurrent MOG-Ab-positive demyelinating syndromes such as MDEM and ADEM-ON. However, clinical evidence is limited for children with ADEM [1,48].

**Prognosis**

The long-term overall outcome of ADEM is usually favorable because most children with ADEM respond to conventional treatment. Full recovery with normal neurological examination occurs in approximately 50% to 80% of patients, and minor neurological deficits, such as clumsiness and mild hemiparesis, are reported in 20% to 30% of patients [1,4,12]. Long-term cognitive and behavioral problems such as lower intelligence quotient, difficulties in executive function, memory impairment, and attention deficits are reported in up to 56% of patients [1,4,9,12]. According to a prior study, 22% of patients with ADEM had seizures during the acute presentation and 16.2% developed epilepsy afterward. Post-ADEM epilepsy was more frequently observed in children with relapsing disease than in those with monophasic disease and in MOG-Ab-positive children than in MOG-Ab-negative cases [49]. Although debate continues whether relapsing ADEM, called MDEM, is MOGAD or possibly NMOSD, the relapsing form has been reported in less than 10% of children with ADEM [6]. Almost a quarter of hospitalized patients with ADEM were in a critical condition and required admission to the PICU, with a mortality rate of 1% to 3% [4,6,34].

**Future perspective**

ADEM is an inflammatory demyelinating disease of the CNS that mostly affects children after viral or bacterial infections, or rarely after various vaccinations. The exact pathogenesis of ADEM remains unclear, although non-specific self-sensitization of reactive T cells against myelin proteins, such as MBP and myelin oligodendrocyte protein, and molecular mimicry of infectious agents are currently considered the predominant pathogenic mechanisms. Despite advances in MOG-Ab and other neurobiological clues, the diagnosis is still based on clinical and radiological findings and the exclusion of other conditions mimicking ADEM. Further studies are needed to identify any biological clues that can define the subtypes of ADEM and distinguish ADEM from other types of ADEM that mimic demyelinating diseases. Since conclusive data on the optimal treatment of ADEM and its outcomes are still lacking, well-designed collaborative multicenter studies are required to achieve the best results and minimize neurological sequelae.

**Conflicts of interest**

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

**ORCID**

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**References**

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A Mixed–Lipid Diet (Medium–Chain and Long–Chain Triglycerides) for Better Tolerability and Efficiency in Pediatric Epilepsy Patients

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Purpose: In the past, the use of medium-chain triglycerides (MCTs) for a ketogenic diet (KD) was expected to improve both patients' and caregivers' adherence to treatment, but many gastrointestinal problems have been reported. Through a calculated partial administration of MCTs in a KD, we aimed to reduce these complications, while maintaining acceptable seizure reduction.

Methods: At a tertiary referral center for pediatric patients with epilepsy, MCT oil was given in a 1:1 ratio with long-chain triglycerides to patients on KDs. Patients who began the diet from February 2019 to February 2020 were reviewed retrospectively, and 47 patients with at least 3 months of follow-up records were enrolled in the study.

Results: Overall, 29.8% of patients on a KD with an adjusted MCT ratio experienced complications, such as gastrointestinal symptoms and behavioral food refusal, compared to 63.0% of prior KD patients. The mean seizure reduction rate was 68.45%±40.61%, which was not significantly different from the comparison group's rate of 64.84%±34.24%.

Conclusion: Adjusted MCT incorporation into a KD showed comparable seizure control results, with better tolerability of the diet.

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

Introduction

The ketogenic diet (KD) has been widely recognized as one of the most effective therapies for drug-resistant epilepsy in the pediatric population [1,2] since its introduction by Wilder [3]. The KD, which involves a restricted diet of high fat and low carbohydrates, is expected to increase ketone body concentrations, which can enhance inhibitory neurotransmission and thereby control seizures to some extent [4]. Several studies have shown that KD therapy is effective for treating drug-resistant epilepsy and metabolic disorders such as glucose transporter 1 (GLUT1) deficiency [5] and pyruvate dehydrogenase deficiency [6] in children and adolescents. Several randomized controlled trials have shown that dietary treatment can reduce seizure frequency by half in 38% to 72% of patients with 3 months of therapy [2,4,7].

There are several types of KDs, with the classical KD comprising...
fat in combination with carbohydrates and protein in specific ratios, ranging from 2:1 to 5:1, and typically utilizing long-chain triglycerides (LCTs) for fat [8]. Adherence to restricted food choices and amounts must be strictly enforced in order to maintain the targeted ketone range, and even minor lapses, such as sugar-containing syrup medication, can compromise treatment efficacy. These dietary restrictions can be challenging for both patients and caregivers, especially for children whose adherence may be inconsistent. Food refusal, limited daily intake, and behavioral problems (e.g., anger and non-acceptance) are common manifestations of adherence problems [9]. Various types of KDs have been designed to improve adherence without compromising the seizure control effects: the modified KD, modified Atkins diet (MAD), low glycemic index treatment (LGIT), and medium-chain triglyceride diet (MCD) [10].

Medium-chain triglycerides (MCTs), such as triglycerides (TG) of octanoic and decanoic acids, are more ketogenic than LCTs, as they lead to the generation of more ketones per kilocalorie of energy. By replacing LCTs in a KD, MCTs can allow more carbohydrate and protein consumption with less total fat, resulting in more acceptable meals and snacks for patients [11]. Huttenlocher et al. [11] first used MCTs for a KD with the expectation of providing a more acceptable diet, and their study in 1971 found that the MCD showed similar seizure reduction rates to the classic KD. Other studies by Schwartz et al. [12] and Neal et al. [13] found no significant difference between the classic KD and MCD when using MCTs with a KD. However, gastrointestinal (GI) problems such as vomiting, bloating, diarrhea, and abdominal pain were common, and MCTs have not been widely used in KDs despite their non-inferior efficacy in seizure control [11-13].

If this high incidence of GI side effects can be offset by modifying the previously used MCD, the advantages of MCTs over LCTs could be utilized more widely. This may be more beneficial for some patients who need more leniency from the classic KD. Both a greater variety of choices of food and larger amounts of food would be desirable for young patients, allowing more freedom of diet and more materials to support ongoing body growth. In the early MCD studies, MCTs comprised 60% of the diet’s total energy, and this amount could have caused the frequently reported GI troubles [11]. Few studies have reported the implementation of MCD and even fewer have discussed any new modifications of the MCD to control the side effects.

After incorporating lower percentages of MCTs than previously reported in other MCD studies, we have observed that patients were able to tolerate the therapeutic diet better than what was expected from past literature reviews.

Subsequently, there have been a small number of studies that have tested other versions of MCDs with lower percentages of MCTs and supplemental LCTs. Along with the levels of ketosis, the amount of total fat and MCTs in various forms of food was also taken into consideration, and a mixed-lipid diet (MLD) with a 1:1 ratio of MCTs and LCTs was tried in a number of patients at our center. By comparing them to previous KD patients, we aimed to investigate the tolerability and efficacy of the MCT and LCT mixed diet, which may become a more feasible KD for pediatric epilepsy patients.

Materials and Methods

1. Patients
Patients from the ages of 6 months to 18 years who initiated a KD at a tertiary referral center between February 2019 and February 2020 were recruited retrospectively by reviewing their medical records, and those who incorporated MCTs into their diet were enrolled in the study. Patients who had been followed for less than 3 months or who had not visited the clinic regularly after starting the diet were excluded.

As the primary endpoint of the study was to assess and analyze the complications of the MCD, patients who started the diet for cognitive or developmental improvement were also included in the study to increase the pool of patients. The small number of recruited MCD patients, with an even smaller number of complications, may have resulted in incomparable analyses.

A cohort of patients on a KD without MCTs was selected from the patients treated at the same tertiary center from 2017 to 2020. Patients’ sex, age at the start of KD, and type of KD were taken into account, and those who had maintained the therapy for less than 3 months were excluded. Patients who were put on the diet for cognitive and developmental reasons were also selected in similar proportions to those of the patients in the MCT diet group.

2. Ketogenic diet
Patients on a KD with MCTs began with one of the various KDs: 4:1, 3:1, 2:1 ratio, MAD, and LGIT. Only after the full implementation of one of these diets were MCTs introduced into the diet, starting with 5% of the total calories. During admission, the amount of MCTs was gradually increased by 5% of the total calories, usually over a 1- to 2-day period. The target MCT quantity was 50% of the total fat amount for the designated KD, with the remaining fat being LCT oil, resulting in a 1:1 ratio of MCTs in quantity. However, the serving amount was limited to 14 g per meal and 52 g per day to minimize potential side effects, and the lower-ketogenic-ratio diets allowed a wider range of food into the diet, reducing the necessary amount of supplementary oil and the
quantity of MCT oil, therefore resulting in a lower amount of MCT oil than the target. When the calories from each type of oil were calculated, the aim was for MCTs to provide approximately 25% to 30% of the total fat calories, and about 20% to 25% of the diet’s total calories. Supplemental vitamins and minerals were fully provided.

If any complications pertaining to the diet arose, such as abdominal pain, vomiting, diarrhea, or other GI symptoms, the amount of MCTs was usually reduced by 10%.

3. Data acquisition
According to the center’s KD protocol, the majority of patients were admitted and evaluated at the start of KD. Patients were regularly followed up at the outpatient clinic after successful diet induction. The admission, hospital stay, and clinical medical charts were reviewed, and patients’ epilepsy status and general condition were evaluated at baseline during admission, as well as at 1, 3, 6, and 9 months at the outpatient clinic.

The primary endpoint of this study was the occurrence of side effects while patients were on the MCT-including KD, including clinical symptoms and laboratory results. Any related findings were categorized as early or late complications based on the time since the start of the KD. Tolerability was determined by the responses of parents or caregivers.

The secondary endpoint of this study was to assess the change in the seizure rate when compared to the baseline seizure frequency at diet initiation, in order to establish whether the MCD had non-inferior efficacy for epilepsy. This was assessed by parental or caregiver seizure records. Another secondary endpoint was any unexpected abnormal laboratory findings regarding the incorporation of MCTs into the KD. Total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and TG levels were compiled. These laboratory results were also compared from baseline to 1, 3 months, and if possible, also for 6 and 9 months. Withdrawals from the dietary treatment at any period were documented, and the reasons for withdrawal were also reviewed.

4. Statistical methods
SPSS version 25.0 for Windows (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. To compare the basic characteristics and seizure outcomes of the MCT group and its comparative cohort group, the Student t-test, chi-square test, Fisher exact test, and Mann-Whitney U test were used. The Fisher exact test was used to compare complications between the two groups, and the Student t-test and, primarily, the Mann-Whitney test were used to analyze the lipid profiles of the two groups. The threshold for statistical significance was set at $P=0.05$.

Results

Fig. 1 depicts how the patients were recruited and grouped for this study. From February 2019 to February 2020, 65 patients on the KD had MCT oil added to their diet, and 49 patients were able to stay on the diet for at least 60 days after starting. In total, 47 patients continued the KD with MCT oil for at least 3 months, 37 for more than 6 months, and 18 for 9 months.

1. Characteristics of the study patients
The study patients’ clinical characteristics are summarized in Table 1. The group was made up of more boys (61.7%) than girls, and the patients ranged in age from 12.4 to 197.6 months. About half of them experienced daily seizures, and the patients with seizures were prescribed an average of $2.47 \pm 1.53$ anti-seizure medications. Several etiologies were suspected as the causes of the patients’ seizures, mainly genetic conditions such as Dravet syndrome, GLUT1 deficiency syndrome, or alterations of genes such as CDKL5, CSTB, DNM1, GRIN1, and KCNQ2. Other etiologies included epilepsy with metabolic causes and structural etiologies such as focal brain lesions, while many patients had undetermined etiologies. It was difficult to match the comparative cohort group in terms of a similar variety of etiologies; however, the two groups showed no significant differences in the etiologies of epilepsy.

![Fig. 1. Flow of patients: study enrollment and follow. MCT, medium-chain triglyceride.](https://doi.org/10.26815/acn.2022.00094)
Twenty-six patients started with the MAD, 16 patients with a 3:1-ratio KD, and one patient each received LGIT, a 2:1-ratio KD, and a 4:1-ratio KD. During the 9-month follow-up period, 10 patients adjusted their diet ratio: five for better tolerability and five for better seizure control or cognitive improvement. The use of MCT oil was maintained during these adjustments.

2. Seizure outcomes
To evaluate short-term seizure outcomes, changes in the seizure rate were measured by comparing the seizure frequency from each time interval to the number of seizures at baseline. As four patients were put on the diet with the expectation of improving their cognitive development, they were excluded from the seizure outcome analysis. At the 3-month follow-up visit, 27 patients (27/43, 62.8%) had more than 90% seizure reduction, and 22 patients (22/43, 51.2%) were seizure-free. Altogether, 86.0% of the patients showed a 50% or greater reduction in seizure frequency at the 3-month follow-up visit. Six months after starting the diet with MCT oil, 37 patients maintained the diet, and 21 patients (21/37, 56.8%) were seizure-free. Furthermore, 70.3% (26/37) were able to reduce their baseline seizure frequency by 90% or more. Thirty-one patients (31/37, 83.8%) had their seizures reduced by 50% or more at the 6-month follow-up interval. At the 9-month interval, corresponding to the last follow-up visit for the study, 18 patients remained, of whom 11 (11/18, 61.1%) had achieved seizure freedom. Twelve patients were able to reduce their baseline seizures by 90% and 16 by 50% or higher.

At the 3- and 6-month follow-ups, the MLD and comparative cohort group showed statistically significant differences in the median values of the seizure reduction rate (100.00%, 50.00%–100.00% vs. 75.00%, 50.00%–99.00%, P = 0.041 at 3 months; and 100.00%, 50.00%–100.00% vs. 66.66%, 50.00%–91.76%, P = 0.027 at 6 months). However, at the last follow-up (after 9 months), the two groups showed no significant difference in the median seizure reduction rate (100.00%, 72.50%–100.00% vs. 90.00%, 61.67%–100.00%, P = 0.403). The overall average seizure reduction rate at the last follow-up for patients who were treated for a minimum of 3 months was 68.45% ± 40.61% in the MLD group and 64.84% ± 34.24% after treatment for a median duration of 6 months in both groups (Table 2). The 43 patients who maintained the KD with MCT oil for at least 3 months were prescribed an average of 2.47 ± 1.53 anti-seizure medications at the time of diet initiation. While 17 (39.5%) of them were able to reduce the number of medications or lower the dosage of the medications, the

Table 1. Characteristics of patients who received a ketogenic diet with MCT oil and the comparative cohort group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MCT oil group (n = 47)</th>
<th>Comparative cohort (n = 27)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at initiation of the ketogenic diet (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–≤ 3</td>
<td>18</td>
<td>11</td>
<td>0.385a</td>
</tr>
<tr>
<td>3–≤ 7</td>
<td>20</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>7–≤ 10</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>&lt; 10</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Age (mo)</td>
<td>59.47 (27.17–81.03)</td>
<td>51.40 (23.83–93.03)</td>
<td>0.987b</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>29:18</td>
<td>16:11</td>
<td>0.979c</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td>0.682²</td>
</tr>
<tr>
<td>Dravet syndrome</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>GLUT1 deficiency syndrome</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Genetic epilepsy</td>
<td>11</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Metabolic causes</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Structural etiology (focal)</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Periventricular leukomalacia</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Unknown etiology</td>
<td>12</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>No. of ASMs</td>
<td>2.47 ± 1.53</td>
<td>2.48 ± 1.42</td>
<td>0.932²</td>
</tr>
<tr>
<td>No. of seizures at initiation</td>
<td>43</td>
<td>24</td>
<td>0.119a</td>
</tr>
<tr>
<td>Daily</td>
<td>21</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Weekly</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Monthly</td>
<td>11</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yearly or less</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or mean ± standard deviation.
MCT, medium-chain triglyceride; GLUT1, glucose transporter 1; ASM, anti-seizure medication.
Fisher exact test; Mann-Whitney U test; Chi-square test.
mean number of anti-seizure medications after MLD was 2.42 ± 1.71, with no significant difference between before and after the diet (P = 0.90). The other KD group also showed no statistically significant change in the mean number of prescribed medications (P = 0.92).

3. Tolerability of dietary treatment

Early complications of dietary therapy occurred in 14 patients during diet implementation or within the first month after diet initiation, with 19 total cases of insufficient oral intake, dehydration, metabolic acidosis, vomiting, or abnormal laboratory results. Following the first month of the diet, three patients experienced weight loss, frequent vomiting, and hypercalciuria, which were recorded as late complications (Table 3). In contrast, 63.0% of the patients in the comparative cohort group (17/27) reported a total of 25 cases of KD-related problems. Vomiting (n = 3), poor oral intake (n = 2), food refusal (n = 2), and single cases of diarrhea, abdominal discomfort, constipation, and several abnormal laboratory findings (n = 9) were noted during the first month after KD induction, and similar cases of GI symptoms and laboratory results were reported, albeit with a lower incidence, during the latter part of KD (Table 3).

In a comparison of the number of reported troubles due to the KD between the MLD group and the non-MLD group, no significant differences were found in any categories in both the early and late stages of the dietary treatment. Taking all the complications into account, the patients from the MLD group reported fewer complications in the later stage of the diet, constituting a significant difference from the comparative group (P = 0.014). Overall, fewer patients experienced KD-related complications in the MLD group during the entire KD process than in the non-MLD (P = 0.005).

These complications, in both the early and later stages of the dietary treatment, contributed to termination of the diet in some patients. Thirteen patients (13/47, 27.7%) discontinued the MCT oil diet during the 3- to 9-month follow-up period; while five of them had suffered from the abovementioned complications, eight patients stopped the diet due to poorer than expected seizure control and either added anti-seizure medications or considered other treatment modalities, such as corpus callosotomy or vagus nerve stimulation. In the comparative cohort group, 16 patients discontinued the KD, half of whom did so due to poor seizure control. Four other patients could not continue the diet because of GI symptoms such as vomiting or abdominal discomfort, two patients due to poor oral intake, and two patients due to the caretaker’s poor adherence to the diet regimen.

4. Changes in the lipid profile after MCT-oil KD

Laboratory results from baseline and follow-up visits of the patients in both groups were collected and statistically analyzed (Table 4). Mean values were obtained from the remaining patients at each follow-up period. While total cholesterol, HDL-C, LDL-C, and non-HDL-C levels all increased during the KD, there was no

Table 2. Ketogenic diet implementation and comparative seizure outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>MCT oil group (n = 47)</th>
<th>Comparative cohort (n = 27)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of ketogenic diet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3:1</td>
<td>17</td>
<td>7</td>
<td>0.865\textsuperscript{a}</td>
</tr>
<tr>
<td>2:1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1.5:1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Modified Atkins diet</td>
<td>26</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Low glycemic index treatment</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Follow-up KD period (mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3</td>
<td>47</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>≥ 6</td>
<td>38</td>
<td>20</td>
<td>(\chi^2 = 0.465, 0.495)</td>
</tr>
<tr>
<td>≥ 9</td>
<td>18</td>
<td>13</td>
<td>(\chi^2 = 0.684, 0.408)</td>
</tr>
<tr>
<td>Seizure outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure reduction rate</td>
<td>68.45 ± 40.61</td>
<td>64.84 ± 34.24</td>
<td>0.352\textsuperscript{a}</td>
</tr>
<tr>
<td>Seizure freedom</td>
<td>21 (48.8)</td>
<td>8 (29.6)</td>
<td>(\chi^2 = 2.522, P = 0.112)</td>
</tr>
<tr>
<td>≥ 90% reduction</td>
<td>26 (60.5)</td>
<td>10 (37.0)</td>
<td>(\chi^2 = 3.644, P = 0.056)</td>
</tr>
<tr>
<td>≥ 50% reduction</td>
<td>34 (79.1)</td>
<td>23 (85.2)</td>
<td>(P = 0.753)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%). MCT, medium-chain triglyceride; KD, ketogenic diet.
\(\textsuperscript{a}\)Fisher exact test; \(\textsuperscript{b}\)Student t-test; \(\textsuperscript{c}\)Chi-square test.

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significant difference between the two groups from baseline to 1 and 3 months. When compared to the MCT oil group, TG levels in the comparative cohort group increased significantly faster at 3 months.

According to the pediatric panel of the National Cholesterol Education Program (NCEP) in the United States, each component of the lipid profile can be categorized into high, borderline, and low levels, and the lipid results of the patients in both groups were analyzed in those terms (Fig. 2). Only 7.7% of the MCT-oil-added patients and 8.7% of the patients in the comparative cohort group had high LDL levels (above 130 mg/dL) at the start of the diet, and this proportion increased throughout the treatment period, ending up with 41.7% and 50% of respective groups having high LDL levels. At baseline, 9.5% and 12.5% of both groups had total cholesterol levels above the acceptable range (200 mg/dL), respectively, and after 9 months of the KD, 46.2% of the MCT-oil group and 62.5% of the comparative cohort group had high total cholesterol levels. Acceptable HDL-C levels (> 45 mg/dL) were found in 68.3% of the patients in the MCT oil group and in 75.0% of the comparative cohort group at baseline; however, this higher percentage in the comparative cohort group changed after 9 months, when the corresponding proportions were 91.7% and 57.1%, respectively.

The NCEP pediatric panel recommends different acceptable TG ranges for children aged 0 to 9 and children aged 10 and up; because the study group mostly comprised children under the age of 10 (40 out of 43), only TG levels in this specific range group were compared. After baseline, 23.7% of patients in the MCT-oil group and 32.0% of those in the comparative cohort group had elevated TG levels (100 mg/dL); by 9 months after KD initiation, these proportions changed to 20.0% and 66.7%, respectively.

Discussion

As the history of MCT oil incorporation into KDs is not short, some previous studies have evaluated its efficacy and clinical applications. Neal et al. [13] conducted a randomized controlled trial demonstrating that the classical KD is not superior to an MCT-based diet in terms of efficacy and tolerability. A prospective long-term study (2 years of follow-up) on KD patients, 79.2% of whom were supplemented with MCT oil, also showed good tolerability and non-inferior efficacy of the diet [14]. However, considering the ability of MCT oil to facilitate relaxation of dietary restrictions, the benefits of using MCT oil over other LCTs were not as prominent as expected. By fine-tuning the MCT oil application in KD, with a 1:1 ratio between MCT oil and LCTs, we aimed to optimize the patients’ KD experience with fewer adverse effects and comparable seizure control.

GI dysfunction such as vomiting and abdominal pain or discom-

Table 3. Early and late complications of ketogenic diets in the two groups

<table>
<thead>
<tr>
<th>Types of complications</th>
<th>MCT oil group (n = 47)</th>
<th>Comparative cohort (n = 27)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early (start–1 mo)</td>
<td>Late (&gt; 1 mo)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>2</td>
<td>1</td>
<td>0.045*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>1</td>
<td>0.056</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
<td>0.008*</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Poor oral intake</td>
<td>7</td>
<td>0</td>
<td>0.472</td>
</tr>
<tr>
<td>Behavioral food refusal</td>
<td>0</td>
<td>0</td>
<td>0.130</td>
</tr>
<tr>
<td>Abnormal laboratory results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Liver enzyme increase</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Acidosis</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>3</td>
<td>0.047*</td>
</tr>
<tr>
<td>Total patients</td>
<td>14</td>
<td>3</td>
<td>0.014*</td>
</tr>
<tr>
<td>Overall cases</td>
<td>20</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Overall patients</td>
<td>14 patients (29.8%)</td>
<td>17 patients (63.0%)</td>
<td>0.005*</td>
</tr>
</tbody>
</table>

MCT, medium-chain triglyceride.

*Fisher’s exact test.

https://doi.org/10.26815/acn.2022.00094
Table 4. Plasma levels of components of the lipid profile at baseline, and after 1 and 3 months of ketogenic diet therapy

<table>
<thead>
<tr>
<th>Plasma level</th>
<th>MCT oil group</th>
<th>Comparative cohort</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1 month</td>
<td>3 months</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>151.7 ± 32.1 (44)</td>
<td>181.0 (44)</td>
<td>185.0 (43)</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>50.0 (43)</td>
<td>51.0 (43)</td>
<td>52.0 (41)</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>84.4 ± 28.3 (40)</td>
<td>115.6 (39)</td>
<td>114.0 (34)</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>95.5 (40)</td>
<td>134.5 (40)</td>
<td>140.0 (37)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>71.0 (43)</td>
<td>92.0 (43)</td>
<td>82.0 (41)</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or median (interquartile range). The number of accounted patients for each mean or median value is noted in parentheses.

MCT, medium-chain triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

a Student t-test; b Mann-Whitney test.
Fig. 2. Percentage of high levels of lipid profile at baseline, and after 1, 3, 6, and 9 months of ketogenic diet. (A) Comparison of percentage of high total cholesterol (≥200 mg/dL) patients. (B) Comparison of percentage of low high-density lipoprotein cholesterol (HDL-C) (<35 mg/dL) patients. (C) Comparison of percentage of high low-density lipoprotein cholesterol (LDL-C) (≥130 mg/dL) patients. (D) Comparison of percentage of high triglyceride (≥100 mg/dL) patients. MCT, medium-chain triglyceride.

many patients and families. Aside from adjusting the ratios of the KD, utilizing MCT oil as an alternative source of fat can be just as effective, despite near-failures or complications in the past. This study demonstrated the possibility of a more tolerable, and thus sustainable, solution for dietary therapy by designing a KD with a 1:1 ratio of MCT and LCT oil.

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

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References


Generalized Tonic–Clonic Seizures after Self-Limited Epilepsy with Centrotemporal Spikes: A Case Series

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Purpose: Patients with self-limited epilepsy with centrotemporal spikes (SLECTS) rarely experience generalized tonic-clonic seizures (GTCS) after remission, and post-remission GTCS has not been thoroughly described in earlier studies. Herein, we describe the clinical and electrographic features of GTCS after a substantial period of seizure freedom in patients with SLECTS.

Methods: This study included six patients (three boys and three girls) diagnosed with SLECTS who later developed GTCS after or near remission. Medical records, including clinical data and serial electroencephalography (EEG) recordings, were retrospectively reviewed for all patients.

Results: Patients’ age at SLECTS onset ranged from 5.2 to 10.2 years (mean, 8.4 years), while seizure cessation was achieved between 8 and 12.2 years. During SLECTS, typical centrotemporal spikes were observed in all patients, and generalized spike-and-wave discharges were observed in three patients. The age at the first episode of subsequent GTCS ranged from 14.4 to 17.3 years (mean, 15.8 years), constituting an average interval of 5.6 years after the last episode of seizures (range, 4.1 to 8.1 years). EEG at subsequent episodes of GTCS revealed generalized discharges in two patients, focal discharges in two other patients, and normal discharges in the remaining two patients. Two patients had multiple episodes of GTCS.

Conclusion: Although rare, GTCS may occur near or after remission in patients with SLECTS, and clinicians should be aware of this. Subsequent GTCS may be a manifestation of idiopathic generalized epilepsy. However, large-scale studies are needed to determine the nature of such episodes of GTCS and their associated risk factors.

Keywords: Epilepsy, rolandic; Seizures; Epilepsy, generalized

Introduction

Self-limited epilepsy with centrotemporal spikes (SLECTS) or benign childhood epilepsy with centrotemporal spikes is the most frequent type of self-limited focal epilepsy, accounting for 15% to 25% of syndromic pediatric epilepsy cases [1,2]. The age of onset ranges from 2 to 12 years, with a peak age between 7 and 9 years. Onset before 2 or after 12 years of age is unusual [3]. Seizures mostly present with focal hemifacial sensorimotor symptoms with brief durations and predominantly occur during sleep. Seizures...
may become focal to bilateral tonic-clonic seizures, which were formerly termed "secondary generalization." Characteristic electroencephalography (EEG) findings include normal background activity with stereotypical centrotemporal spikes. SLECTS shows an excellent prognosis, where patients usually enter remission within 1 to 3 years from onset, and most patients are free of seizures after the age of 15 to 16 years [4,5].

The occasional occurrence of generalized tonic-clonic seizures (GTCS) after SLECTS has been mentioned in the literature. The subsequent presentation of generalized seizures, such as absence seizures, and less often, GTCS, was reported to occur in 1% to 2% of patients with SLECTS. A few published studies have reported GTCS following SLECTS [5-7]. Loiseau et al. [8] described that SLECTS was associated with a 10-fold higher relative risk of GTCS than observed in the normal population. However, other authors consider subsequent GTCS to be an independent de novo event [9,10]. Nevertheless, to date, there is a lack of detailed descriptions of patients with subsequent GTCS after SLECTS. In addition, the pathophysiological mechanisms of such seizures have yet to be determined.

In accordance with the favorable prognosis of SLECTs, most patients with SLECTS present infrequent seizures, relatively short periods of disease, and a good response to antiseizure medication (ASM). However, we recently observed rare occurrences of GTCS in patients near or after SLECTS remission. Some experienced a single GTCS episode, as in most previous studies, whereas others experienced multiple seizure episodes, sometimes with generalized epileptiform discharges. Thus, we retrospectively reviewed the characteristics of six children who developed GTCS after SLECTS. This study aimed to inform clinicians that GTCS may occur in patients with SLECTS, albeit rarely. In addition, we intend to provide detailed descriptions of our experiences to improve the clinical understanding of subsequent GTCS.

Materials and Methods

Among patients from the pediatric neurology departments of Seoul National University Bundang Hospital and Seoul National University Children’s Hospital, six patients (three boys and three girls) from 1998 to 2021 were identified as having GTCS after SLECTS. A few published studies have reported GTCS following SLECTS [5-7]. Loiseau et al. [8] described that SLECTS was associated with a 10-fold higher relative risk of GTCS than observed in the normal population. However, other authors consider subsequent GTCS to be an independent de novo event [9,10]. Nevertheless, to date, there is a lack of detailed descriptions of patients with subsequent GTCS after SLECTS. In addition, the pathophysiological mechanisms of such seizures have yet to be determined.

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Results

Six SLECTS patients (three boys and three girls) developed GTCS at an average of 5.6 years after the last episode of seizures (range, 4.1 to 8.1 years). Detailed clinical descriptions of the patients are provided below.

1. Case reports

Patient 1 (female) developed focal motor seizures during sleep at 5.2 years of age. The semiology included unilateral upper extremity stiffening and clonic movements. Focal to bilateral tonic-clonic seizures were sometimes observed in later episodes. She had a history of simple febrile seizures at 3 years of age. The patient had no family history of febrile seizures or epilepsy. The patient achieved her developmental milestones. Physical and neurological examinations revealed no abnormalities. Her EEG revealed frequent high-voltage spike-and-wave discharges from C3–T3 and C4–T4, which were activated during sleep. Brain magnetic resonance imaging (MRI) revealed no remarkable findings. Upon diagnosis of SLECTS, carbamazepine was administered. She became seizure-free at the age of 9 years, and ASMs were discontinued at 14 years of age. Six months after withdrawal, the patient experienced daytime GTCS. At that time, her EEG revealed generalized bursts of spike-and-wave discharges. Thus, we retrospectively reviewed the serial EEG recordings and confirmed the presence of generalized discharges. The patient continued to have occasional GTCS. After 10 years of treatment, she achieved seizure remission.

Patient 2 (female) developed focal motor seizures at 1 year and 6 months of age. The semiology included bilateral tonic-clonic seizures. Her EEG revealed frequent high-voltage spike-and-wave discharges from C3–T3 and C4–T4, which were activated during sleep. Brain magnetic resonance imaging (MRI) revealed no remarkable findings. Upon diagnosis of SLECTS, carbamazepine was administered. She became seizure-free at the age of 9 years, and ASMs were discontinued at 14 years of age. Six months after withdrawal, the patient experienced daytime GTCS. At that time, her EEG revealed generalized bursts of spike-and-wave discharges. Thus, we retrospectively reviewed the serial EEG recordings and confirmed the presence of generalized discharges. The patient continued to have occasional GTCS. After 10 years of treatment, she achieved seizure remission.

Patient 3 (female) developed focal motor seizures at 2 years of age. The semiology included bilateral tonic-clonic seizures. Her EEG revealed frequent high-voltage spike-and-wave discharges from C3–T3 and C4–T4, which were activated during sleep. Brain magnetic resonance imaging (MRI) revealed no remarkable findings. Upon diagnosis of SLECTS, carbamazepine was administered. She became seizure-free at the age of 9 years, and ASMs were discontinued at 14 years of age. Six months after withdrawal, the patient experienced daytime GTCS. At that time, her EEG revealed generalized bursts of spike-and-wave discharges. Thus, we retrospectively reviewed the serial EEG recordings and confirmed the presence of generalized discharges. The patient continued to have occasional GTCS. After 10 years of treatment, she achieved seizure remission.

Patient 4 (male) developed focal motor seizures at 1 year and 6 months of age. The semiology included bilateral tonic-clonic seizures. His EEG revealed frequent high-voltage spike-and-wave discharges from C3–T3 and C4–T4, which were activated during sleep. Brain magnetic resonance imaging (MRI) revealed no remarkable findings. Upon diagnosis of SLECTS, carbamazepine was administered. He became seizure-free at the age of 9 years, and ASMs were discontinued at 14 years of age. Six months after withdrawal, the patient experienced daytime GTCS. At that time, his EEG revealed generalized bursts of spike-and-wave discharges. Thus, we retrospectively reviewed the serial EEG recordings and confirmed the presence of generalized discharges. The patient continued to have occasional GTCS. After 10 years of treatment, he achieved seizure remission.

Patient 5 (female) developed focal motor seizures at 1 year and 6 months of age. The semiology included bilateral tonic-clonic seizures. Her EEG revealed frequent high-voltage spike-and-wave discharges from C3–T3 and C4–T4, which were activated during sleep. Brain magnetic resonance imaging (MRI) revealed no remarkable findings. Upon diagnosis of SLECTS, carbamazepine was administered. She became seizure-free at the age of 9 years, and ASMs were discontinued at 14 years of age. Six months after withdrawal, the patient experienced daytime GTCS. At that time, her EEG revealed generalized bursts of spike-and-wave discharges. Thus, we retrospectively reviewed the serial EEG recordings and confirmed the presence of generalized discharges. The patient continued to have occasional GTCS. After 10 years of treatment, she achieved seizure remission.

Patient 6 (female) developed focal motor seizures at 1 year and 6 months of age. The semiology included bilateral tonic-clonic seizures. Her EEG revealed frequent high-voltage spike-and-wave discharges from C3–T3 and C4–T4, which were activated during sleep. Brain magnetic resonance imaging (MRI) revealed no remarkable findings. Upon diagnosis of SLECTS, carbamazepine was administered. She became seizure-free at the age of 9 years, and ASMs were discontinued at 14 years of age. Six months after withdrawal, the patient experienced daytime GTCS. At that time, her EEG revealed generalized bursts of spike-and-wave discharges. Thus, we retrospectively reviewed the serial EEG recordings and confirmed the presence of generalized discharges. The patient continued to have occasional GTCS. After 10 years of treatment, she achieved seizure remission.
wave discharges. She was diagnosed with possible idiopathic generalized epilepsy (IGE), for which valproic acid (VPA) was administered. She had three more episodes of daytime GTCS until she was 21 years old, and no further seizures were reported until the last follow-up conducted at 29 years of age.

Patient 2 (female) experienced GTCS 30 minutes after falling asleep at 7 years of age. The patient had a history of simple febrile seizures at 18 months of age. She had a positive family history of febrile seizures (maternal uncle) and epilepsy (father and paternal aunt; specific syndrome information was not available). The patient did not exhibit any neurodevelopmental problems. Physical and neurological examinations did not reveal any abnormalities. EEG revealed spikes or spike-wave discharges from C3 and C4. Brain MRI findings were normal. Oxcarbazepine (OXC) was administered, and she was seizure-free from the age of 8 years. OXC was withdrawn when she was 12 years old. At 16 years of age, she developed daytime GTCS while awake. Her EEG revealed frequent generalized spike- or polyspike-wave discharges. Suspecting IGE, levetiracetam (LEV) was administered. No further seizures were reported until the age of 17 years.

Patient 3 (male) developed focal motor seizures at the age of 9.8 years. He had a tonic deviation of the unilateral face during sleep, followed by focal to bilateral tonic-clonic seizures. His past and family histories were unremarkable, and his developmental profile was normal. The EEG findings were abnormal, with spike-wave discharges at C3-T3 and C4-T4, and the brain MRI findings were normal. After establishing the diagnosis of SLECTS, OXC was administered. The patient was seizure-free from the age of 10 years, and OXC was discontinued at 13 years of age. At 17 years of age, the patient developed daytime GTCS. The EEG findings were normal. VPA was prescribed to prevent GTCS. Two more episodes of GTCS occurred during treatment, and he was seizure-free at the last follow-up conducted at the age of 18 years.

Patient 4 (female) developed focal motor seizures while taking a nap at 10.2 years of age. The semiology included clonic movement of one side of her face, which propagated to the upper extremities. Identiﬁcal episodes occurred on several occasions, sometimes with focal to bilateral tonic-clonic seizures. She had a negative personal history and an unremarkable family history. The patient showed normal psychomotor development. EEG revealed high-voltage spikes or spike-and-wave discharges from C4-T4 during sleep, and brain MRI revealed no abnormal findings. After being diagnosed with SLECTS, OXC was administered. A year later, when she was 11 years old, she was seizure-free, but presented clinically with abrupt and clear impairment of consciousness and electronically with generalized 3-Hz spike-wave discharges. Centrotemporal spikes persisted at this time. VPA was administered instead of OXC until electrographic and clinical normalization of both SLECTS and childhood absence epilepsy (CAE). During ASM tapering, the patient developed daytime GTCS. EEG revealed a few sharp wave discharges from F3 and F4. LEV was administered, and no further seizures were observed until the last follow-up conducted at 16 years of age.

Patient 5 (male) experienced a focal seizure at 8.11 years of age. He presented with focal motor seizures and tonic contraction of the right face during sleep. He experienced a simple febrile seizure at years of age and had an unremarkable family history. His neurodevelopment was normal, and the neurological examination results were unremarkable. EEG recordings showed spike-wave discharges from C3–T3, and brain MRI ﬁndings were normal. After being diagnosed with SLECTS, OXC was administered. The patient was seizure-free from 11 years of age, and OXC was withdrawn after normalization of EEG at 14 years of age. When the patient was 15 years old, he developed daytime GTCS. At the time of evaluation, the EEG ﬁndings were normal. VPA was administered, and no further seizures occurred until the last follow-up conducted at 17 years of age.

Patient 6 (male) developed GTCS during sleep at 8.9 years of age. His past medical history was unremarkable, and his family history was negative. The patient exhibited a normal developmental proﬁle. EEG revealed high-voltage spike-wave discharges from C3–T3 and C4–T4, and brain MRI revealed no abnormal ﬁndings. The neurological examination results were normal. After being diagnosed with SLECTS, OXC was administered. He became seizure-free at 9 years of age. However, because of persistent centrotemporal spikes on EEG, ASMs were continued. When the patient was 14.4 years of age, he developed daytime GTCS. EEG revealed spikes or sharp wave discharges from Fp2–F8 or Fp1–F7. After replacing OXC with VPA, the patient remained seizure-free until the last follow-up conducted at 16 years of age.

2. Clinical characteristics
The general characteristics of the patients are summarized in Table 1. A history of febrile seizures was found in three patients, and a positive family history was observed in one patient. Patient 2 had a family history of febrile seizures and epilepsy within second- and third-degree relatives. All six patients’ neurodevelopmental proﬁles were normal. The age of onset for SLECTS ranged from 5.2 to 10.2 years (mean, 8.4 years). The age at the first subsequent GTCS ranged from 14.4 to 17.3 years (mean, 15.8 years), occurring after remission of SLECTS in three patients and near remission in the other three. The mean interval between the last seizure in SLECTS and the onset of subsequent GTCS was 5.6 years, ranging from 4.1 to 8.1 years. The SLECTS seizure types included focal motor sei-
zures in four children; all had at least once developed focal to bilateral tonic-clonic seizure, whereas isolated GTCS during sleep occurred in two other children. In all cases, the seizures were sleep-related. Patient 4 had a concomitant absence seizure 1 year after the onset of SLECTS.

Throughout SLECTS, fewer than five seizures were observed in four patients, while the two other children experienced six to 10 episodes, respectively. Four patients presented with solitary GTCS episodes, while the two other children had three and four episodes, respectively.

3. EEG characteristics
The features of the EEG recordings are summarized in Table 2. Typical centrotemporal spikes on EEG were found in every patient during SLECTS. Three patients showed generalized spike-and-wave discharges before subsequent GTCS. Among them, generalized 3-Hz spike-wave discharges were also revealed in one patient who had a clinical absence seizure. At the onset of subsequent GTCS, the centrotemporal spikes disappeared. Two patients showed generalized spike-waves on EEG, while epileptiform discharges from the frontal lobe were observed in two patients and normal EEG findings were observed in two other patients.

Discussion
We described six patients with SLECTS who experienced GTCS after being seizure-free. These children had some common features. All six patients showed electrographically and clinically typical SLECTS at onset, such as sleep-related seizures in children with normal neurodevelopment, characteristic EEG recordings, and the absence of structural brain abnormalities.

Additionally, at the time of evaluation for subsequent GTCS, the patients showed changes in electrographic and clinical features from their previous SLECTS. Every episode occurred during the day, without a sleep association, and centrotemporal spikes no longer existed on EEG. All patients except one were off medications at the time of the first subsequent GTCS. SLECTS disappeared between 8 and 12 years of age in our patients, which is consistent with previous reports stating that the resolution of seizures is achieved by the age of 16 [3-5,12]. Three patients did not achieve complete remission by definition; however, they had subsequent GTCS close to the upper limit of the remission age.

The later occurrence of GTCS in our patients with SLECTS was unexpected, particularly in situations where the children were thought to be in a state of post-remission or near remission from SLECTS. However, we encountered a few patients with subsequent GTCS in recent years, although this has scarcely been reported in the literature. The presentation of GTCS after SLECTS was first reported in 1972 [13]. Blom et al. [13] performed a retrospective follow-up study of 40 patients aged > 15 years with a history of SLECTS. They described a girl who had one episode of GTCS at 16 years of age, 3 years after the discontinuation of ASMs. However, clinical data, such as age at the onset of SLECTS, seizure semiology, past medical history, and electrographic recordings, were not documented. Loiseau et al. [8] conducted a more extensive, long-term study, in which 168 patients with SLECTS were followed up for 7 to 30 years. While 165 of 168 patients showed complete remission, three experienced generalized seizures a few years after recovery from SLECTS [8].

A 34-year-old woman presented with one episode of GTCS 24 years after ASM withdrawal. Similar to our cases, an 18-year-old girl whose ASM was discontinued at 12 years of age experienced a single GTCS event. Another woman had two episodes of generalized seizures at 22 years of age, 10 years after ASM withdrawal. The authors concluded that concerning the incidence of GTCS in the community, the relative risk of such seizures is 10-fold after SLECTS, making them unlikely to occur.
be distinct entities. More recently, 29 patients with SLECTS were prospectively followed up for 12 to 17 years in a Dutch study of childhood epilepsy [14]. In a Dutch cohort of children with SLECTS, three developed GTCS after having a seizure-free interval of at least 6 months during their 15 years of follow-up. Further details of these patients with subsequent GTCS have not yet been documented. Although rare, our findings on subsequent GTCS after SLECTS are supported by observations from earlier reports. Unfortunately, descriptions of subsequent GTCS are relatively brief, as most previous studies aimed to investigate the long-term outcomes of SLECTS. Moreover, such issues seem to be overlooked by physicians, probably because of their rarity and favorable prognosis. Thus, we attempted to provide more detailed descriptions of our patients’ clinical and electrographic features and inform pediatric neurologists that although GTCS is rare, it can be observed after being seizure-free from SLECTS.

The authors emphasized the importance of detailed seizure descriptions since they first suspected more than one epilepsy syndrome at different times. The authors suggested the possibility of a pathophysiological relationship with a genetic predisposition. Within a broader scope, cases of coexistent focal and generalized epilepsy have also been reported by several authors. Twelve cases of CAE in patients with localization-related epilepsy were reported by Sofue et al. [19] Among those with focal seizures, four had frontal lobe epilepsy, two had occipital lobe epilepsy, and one was diagnosed with temporal lobe epilepsy, while the types of seizures were undetermined in the remaining five patients. Jeha et al. [20] documented seven patients with focal and IGE. Four patients showed electrographically and clinically proven focal and generalized epilepsy, while the remaining three patients had only focal seizures recorded, but developed clinically suspicious generalized epilepsy. The authors emphasized the importance of detailed seizure descriptions since they first suspected more than one epilepsy syndrome due to the coexistence of auras preceding focal impaired awareness seizures, along with sudden-onset GTCS.

Other types of focal epilepsy may follow the remission of SLECTS. Guerrini et al. [21] reported two cases of idiopathic photosensitive occipital epilepsy in patients who recovered from SLECTS. These cases suggest that two different epilepsy syndromes can appear in the same patient. However, the pathophys-

Table 2. EEG features of the patients

<table>
<thead>
<tr>
<th>Case</th>
<th>EEG at onset of SLECTS</th>
<th>G-spW prior to subsequent GTCS</th>
<th>EEG at onset of subsequent GTCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C3-T3 or C4-T4 spW</td>
<td>No</td>
<td>G-spW</td>
</tr>
<tr>
<td>2</td>
<td>C3 or C4 spW</td>
<td>Yes</td>
<td>G-spW</td>
</tr>
<tr>
<td>3</td>
<td>C3-T3 or C4-T4 spW</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>C4-T4 spW</td>
<td>Yes</td>
<td>F3 or F4 SW</td>
</tr>
<tr>
<td>5</td>
<td>C3-T3 spW</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>6</td>
<td>C3-T3 or C4-T4 spW</td>
<td>Yes</td>
<td>Fp2-F8 or Fp1-F7 sp or SW</td>
</tr>
</tbody>
</table>

EEG, electroencephalography; SLECTS, self-limited epilepsy with centrotemporal spikes; G-spW, generalized spike-wave; GTCS, generalized tonic–clonic seizure; spW, spike-wave; SW, sharp wave; sp, spike.
ology of this co-occurrence has not yet been elucidated. This seems more likely to be a distinct form of epilepsy that occurs independently, although more cases with detailed clinical information are necessary for further investigations.

Among the various electrographic and clinical features of our cases, we observed generalized epileptiform discharges in three patients with SLECTS. Similar findings were described in a previous study, in which 11 out of 12 patients with localization-related epilepsy showed generalized spike-waves prior to a later onset of CAE [19]. These generalized epileptiform discharges in focal epilepsy syndrome may predispose patients to the transition to GTCS. However, generalized spike-wave complexes are sometimes found in children with SLECTS and other focal epilepsies such as childhood epilepsy with occipital paroxysms [6,10,22]. Thus, there is insufficient support to assume that the presentation of generalized discharges before the occurrence of GTCS is a predictive factor.

In our patients, generalized epileptiform discharges, focal abnormalities, and normal findings were revealed on EEG at the time of subsequent GTCS evaluation. However, none of the patients showed 3 to 6 Hz spike- and polyspike-wave discharges on interictal EEG, a characteristic feature of juvenile myoclonic epilepsy. Although focal epileptiform discharges were observed in two of our patients, the semiologic features were primary generalized seizures without evidence of focal seizure onset. In fact, the existence of focal EEG abnormalities is common in IGE and has been found to be observed in about one-third of patients with IGE in previous studies [23]. Therefore, those patients with focal interictal EEG features can still be associated with IGE. In the aforementioned study by Loiseau et al. [8], EEG recordings upon GTCS were only noted in two out of three patients with GTCS after SLECTS. One patient with subsequent GTCS at the age of 34 years showed EEG without paroxysms, whereas the other 22-year-old patient had diffuse, erratic sharp waves on EEG. A large amount of EEG data must be collected to detect significant common electrographic features.

In this study, we sought to describe patients’ clinical and electrographic findings in detail, which were lacking in previous research. Such descriptions are essential to identify the cause of sequential GTCS for precise evaluation, diagnosis, and treatment. We have also thoroughly reviewed the previous literature to corroborate our findings. However, some limitations of this study should be mentioned. Due to the descriptive nature of the case series, risk factors and possible pathophysiologic mechanisms were not analyzed. Another limitation is that although the diagnosis of SLECTS and IGE in our patients was based on their electrographic and clinical characteristics, the findings of generalized EEG abnormalities in SLECTS and focal EEG features in IGE should be interpreted cautiously. Generalized spike-and-wave discharges are sometimes observed in patients with localization-related epilepsy and, likewise, focal discharges may be present in patients with generalized epilepsy. Therefore, serial EEG results and characteristic clinical manifestations should be considered upon diagnosis. In addition, our study included a small number of patients, who may not be representative of a larger group of patients. Further studies with a larger number of patients and longer follow-up duration would greatly improve our understanding of subsequent GTCS and help discover the associated risk factors.

In conclusion, although complete remission of SLECTS has been taken for granted for many years, we observed the subsequent occurrence of GTCS after seizure-free intervals of several years. Although not yet clarified, this form of GTCS may be a manifestation of a different epileptic syndrome, such as IGE. Lastly, pediatric neurologists who treat patients with SLECTS should be aware of the possibility of GTCS occurrence, even after several years of freedom from seizures.

Conflicts of interest

Jieun Choi is an associate editor, Anna Cho, Jong-Hee Chae and Ki Joong Kim are editorial board members of the journal, but they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Author contribution

Conceptualization: HJK, YJK, SYK, AC, HK, BCL, HH, JHC, JC, and KJK. Data curation: HJK, YJK, SYK, AC, HK, BCL, HH, JHC, JC, and KJK. Formal analysis: HJK, YJK, AC, and HK. Methodology: HJK, YJK, AC, and HK. Project administration: HJK. Visualization: HJK. Writing-original draft: HJK. Writing-review & editing: HJK and HK.

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References


Assessment of Parenting Attitudes by Children and Adolescents with Migraine

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Purpose: We aimed to investigate the parenting attitudes reported by patients and their relationships with the characteristics of headaches in children and adolescents with migraine.

Methods: We conducted a retrospective review of medical records of children and adolescents with migrainous headaches (n=115; 59.1% female; mean age, 11.89±2.00 years). Children evaluated parental attitudes using the Parenting Attitude Test-Youth (PAT-Y), which comprises eight subscales and four newly devised secondary subscales. Headache severity was calculated by the visual analog scale (VAS), monthly frequency (MF), and VAS×MF/4 (VF). The scores of PAT-Y subscales and the correlations between PAT-Y scores and headache severity were analyzed by age group and sex. Scores for children’s depression inventory, childhood behavior checklists, and an attention deficit hyperactivity disorder scale were also analyzed.

Results: In the elementary school age group, VAS was weakly negatively correlated with the “achievement press” (r=-0.28, P<0.05) and “high expectation” (r=-0.25, P<0.05) attitudes, and VF was weakly negatively correlated with “achievement press” (r=-0.32, P<0.05), “punishment” (r=-0.27, P<0.05), and “high expectation” (r=-0.29, P<0.05). In the middle-school age group, MF and VF were moderately positively correlated with the “achievement press” attitude (r=0.48, P<0.01 and r=0.48, P<0.01, respectively), VF was weakly positively correlated with the “neglectful” attitude (r=0.31, P<0.05), and MF was weakly positively correlated with scores for depression (r=0.29, P<0.05) and internalized problems (r=0.31, P<0.05).

Conclusion: Parenting attitudes perceived by children and adolescents with migrainous headaches varied by age, and some parenting attitudes were related to headache severity. Education on age-appropriate parenting attitudes may help cope with migrainous headaches.

Keywords: Headache; Child; Migraine disorders; Parenting; Attitude
Introduction

Headache is one of the most common neurological symptoms in children. Among the various causes of recurrent acute headaches, migrainous headaches are a common condition without organic causes. The prevalence of pediatric migraine was reported to be 7.7% to 9.1% [1,2], with 4% to 11% in children 7 to 11 years of age and up to 8% to 23% in adolescents [1-4]. The prevalence is similar in both sexes, but pediatric migraine is more common in girls before adolescence [2]. Although migraine is usually a benign condition, uncontrolled headaches can cause various impairments in activities of daily living.

Parenting attitudes refer to the behavioral patterns and attitudes of primary caregivers that manifest when raising children. Parenting attitudes tend to be consistent during parenting [5], although they may influence or be influenced by disease-related attitudes or behaviors of children with migraine. Researchers have classified parenting attitudes in several ways, mainly using dimensional approaches [6-9]. The most commonly referenced parenting attitude types, as suggested by Baumrind [10] (1971) are authoritative, authoritarian, permissive, and neglectful attitudes, based on the warmth and control dimensions [11]. One of the well-known methods of assessing parenting attitudes is the Parental Attitudes Scale (S) developed by Lamborn et al. [12] (1991), which consists of 26 items. In Korea, both the Parenting Attitude Test (PAT) (assessed by the parent) and the Parenting Attitude Test-Youth (PAT-Y) (assessed by youth) are tools that consider the cultural background of Korea [13].

There are few studies on parenting attitudes toward children with migrainous headaches. Studies have shown that parents of chronic migraine patients have higher oppressive-authoritarian attitudes than those of patients with other types of headache [14], and are more sensitive and overprotective regarding their children’s health problems [15]. Higher age of patients was associated with negative parenting styles [14,16,17]. Previous studies on the relationship between headache characteristics and parenting attitudes have shown that the ambivalent attachment style was associated with high attack frequency and pain intensity in children with migraine [18]. However, other studies found no significant relationships between headache severity and parenting attitudes [14]. Nonetheless, detailed reports on the parenting attitudes of children with migraine or on differences according to children’s age group remain scarce. Evaluating parenting attitudes from the perspective of children can provide valuable information for understanding headache-related behaviors or for the provision of family counseling.

In the present study, we investigated parenting attitudes as perceived by children with migraine and investigated the relationship between headache severity and parenting attitudes. We hypothesized that the parental attitudes perceived by youth may be different in children and teenagers. The analyses were first performed among children of all ages and then separately for elementary-school age group (ESAG) and middle-school age group (MSAG).

Materials and Methods

1. Patients

   We retrospectively reviewed the data of patients treated between March 2014 and November 2019 at the Pediatric Department of Hanyang University Guri Hospital. The inclusion criteria were patients 8 to 15 years of age who were diagnosed with migraine or probable migraine and underwent testing with a battery of behavioral checklists, including the PAT-Y. We excluded patients with migraine-related episodic syndrome.

2. Clinical data

   Migraine was diagnosed based on each patient’s history, physical examination, and neurological examination. For clinical data, age, sex, and characteristics of headache were analyzed. In the present study, we included patients diagnosed with migraine with aura, migraine without aura, and probable migraine. The diagnosis of migraine was re-evaluated during data analysis based on the International Classification of Headache Disorders, third edition [19].

   Headache severity was calculated by visual analog scale (VAS) (range, 1-10; no pain, 0; worst pain, 10), monthly frequency (MF) (number of times of headache occurrence per month), and VAS × MF/4 (VF) score. This study protocol was approved by the Institutional Review Board of Hanyang University Guri Hospital (IRB reference no: GURI 2022-01-018). Written informed consent by the patients was waived due to a retrospective nature of our study.

3. Behavioral scales

   1) Parenting Attitude Test-Youth

   The PAT-Y was developed by Lim and Lee [13] to evaluate parents’ parenting attitudes, which are estimated by children using items that are highly related to emotional exchange and behavioral expression between parents and children. It consists of 43 items, each of which is answered on a 5-point Likert scale, and has the following eight subscales for parenting attitudes [13]: “supportive expression,” “rational explanation,” “achievement press,” “high involvement,” “punishment,” “superintendence,” “high expectation,”
and “inconsequence.” The PAT-Y provides a raw score, percentile scores, and appropriate percentile ranges for each scale. After obtaining scores for the eight primary subscales, we recalculated them into four secondary subscales, corresponding to authoritative, authoritarian, permissive, and neglectful attitudes. Therefore, 12 subscales were used for the analysis in the present study.

2) Korean Children’s Depression Inventory
The Korean Children’s Depression Inventory (K-CDI) is a self-reported scale used to evaluate the emotional, cognitive, and behavioral symptoms of depression in children and adolescents. It consists of a total of 27 items, and a score of ≥ 22 is considered to indicate depression. In the present study, the total score was used for analysis [20].

3) Korean Child Behavior Checklists 6-18
The Korean Child Behavior Checklists 6-18 (K-CBCL 6-18) are used for early identification and diagnosis by evaluating emotional and behavioral problems in children and adolescents using reports from primary caregivers. There are eight subscales within the problem behavior scale: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, delinquent behavior, and aggressive behavior. These subscales can be grouped into two higher-order factors, known as internalizing and externalizing problems. In the present study, percentile scores of internalizing and externalizing problems scales were used for analysis [21,22].

4) Korean Attention Deficit Hyperactivity Disorder Rating Scale-IV
The Korean Attention Deficit Hyperactivity Disorder Rating Scale-IV (K-ARS-IV) [23,24] consists of 18 items with 4-point scales (0–3). The total score of odd-numbered items measures attention deficit symptoms, and the total score of even-numbered items measures hyperactivity-impulsivity symptoms. If the total score is ≥ 19 based on the parental evaluation and ≥ 17 according to the teacher’s evaluation, a child is considered to have attention deficit hyperactivity disorder (ADHD) [25]. In the present study, parental evaluation was conducted, and the total score was used for the analysis.

4. Statistical analysis
The demographic characteristics of the study population are presented as mean ± standard deviation and range for continuous variables and as frequency (percentage) for categorical variables. The independent two-sample t-test was performed to compare differences in demographic and behavioral scales in total and by age group. Pearson correlation analysis was performed to analyze the relationships between behavioral scales and headache severity (VAS, MF, and VF). The statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). A P < 0.05 was considered statistically significant.

Results
1. Clinical characteristics
In total, 115 patients were finally included in the analysis (female, 59.1%; mean age, 11.89 ± 2.00 years). The 62 children attending elementary school (mean age, 10.32 ± 1.30 years; range, 8 to 12) and 53 adolescents attending middle school (mean age, 13.71 ± 0.66 years; range, 13 to 15) were grouped as the ESAG and the MSAG, respectively.

The mean MF of headaches was 12.93 ± 10.03 times/month (range, 0.2 to 28), and the mean VAS was 5.78 ± 1.92 (range, 2 to 10). The mean VF score was 18.33 ± 16.47 (range, 0.2 to 70). Details of the characteristics are presented in Table 1.

2. Behavioral scales
1) PAT-Y
The mean percentile scores for the eight primary parenting attitude subscales ranged from 46 to 60 (ESAG, 50 to 58; MSAG, 43 to 63). The mean percentile scores for four secondary subscales ranged from 49 to 55 (ESAG, 50 to 58; MSAG, 43 to 58). The mean distributions were generally in or around the middle range. The mean scores were more widely distributed in the MSAG than in the ESAG (Supplementary Table 1).

In all age groups, the mean percentile of “supportive expression” was significantly higher in males than in females (57.13 ± 28.82 vs. 43.22 ± 28.08, P = 0.011); in particular, the ESAG (63.33 ± 22.91 vs. 44.56 ± 30.70, P = 0.009) showed significantly higher scores in males. In the MSAG, “achievement press” was significantly higher in males than in females (59.71 ± 18.07 vs. 41.75 ± 26.36, P = 0.014). Supplementary Table 1 presents the results in detail according to age group.

Overall, the scores for positive parenting items as perceived by the patients tended to be higher in the ESAG than in the MSAG, and the scores for negative parenting items tended to be higher in the MSAG than in the ESAG. In particular, the mean percentile scores for “rational explanation” (54.35 ± 30.66 vs. 43.30 ± 29.65, P = 0.048) and “authoritative parenting” (54.11 ± 27.48 vs. 43.33 ± 27.91, P = 0.04) attitudes were higher in the ESAG than in the MSAG, and that for “high expectation” (46.24 ± 30.26 vs. 61.06 ± 26.71, P = 0.007) was significantly higher in the MSAG.
9.51 ± 6.27, \( P = 0.029 \)) of the mean CDI score was significantly higher in the MSAG than in the ESAG (13.28 ± 7.06 vs. 9.68 ± 7.54, \( P = 0.01 \) (Supplementary Table 2)).

The mean percentile score for internalizing problems in the K-CBCL showed no significant difference based on age group or sex. However, the mean percentile score for externalizing problems in the MSAG was significantly higher than that of the ESAG (66.92 ± 25.31 vs. 56.42 ± 26.00, \( P = 0.032 \) (Supplementary Table 2)).

In all age groups, the mean score for inattention (4.85 ± 5.00 vs. 3.24 ± 3.48, \( P = 0.045 \)), hyperactivity-impulsivity (2.89 ± 3.48 vs. 1.40 ± 2.18, \( P = 0.006 \)), and ADHD-total (7.74 ± 8.09 vs. 4.64 ± 5.24, \( P = 0.014 \)) were significantly higher in males than in females. The mean score of ADHD scales was not significantly different according to sex in the ESAG. However, in the MSAG, the mean scores for inattention (6.71 ± 5.90 vs. 3.78 ± 3.58, \( P = 0.029 \)), hyperactivity-impulsivity (3.76 ± 4.12 vs. 1.42 ± 2.10, \( P = 0.008 \)), and ADHD-total (10.47 ± 9.70 vs. 5.19 ± 5.26, \( P = 0.013 \)) were significantly higher in males than in females (Supplementary Table 2).

3) Correlation between PAT-Y and headache severity
In all age groups, there was no clear correlation between the frequency and intensity of headache and parenting attitudes, with only very weak, significantly negative correlations between MF and the “authoritative parenting” attitude (\( r = –0.19, P < 0.05 \)) and between VF and the “rational explanation” attitude (\( r = –0.19, P < 0.01 \) (Table 2)).

In all age groups, the mean score for inattention (4.85 ± 5.00 vs. 3.24 ± 3.48, \( P = 0.045 \)), hyperactivity-impulsivity (2.89 ± 3.48 vs. 1.40 ± 2.18, \( P = 0.006 \)), and ADHD-total (7.74 ± 8.09 vs. 4.64 ± 5.24, \( P = 0.014 \)) were significantly higher in males than in females. The mean score of ADHD scales was not significantly different according to sex in the ESAG. However, in the MSAG, the mean scores for inattention (6.71 ± 5.90 vs. 3.78 ± 3.58, \( P = 0.029 \)), hyperactivity-impulsivity (3.76 ± 4.12 vs. 1.42 ± 2.10, \( P = 0.008 \)), and ADHD-total (10.47 ± 9.70 vs. 5.19 ± 5.26, \( P = 0.013 \)) were significantly higher in males than in females (Supplementary Table 2).

2) K-CDI, K-CBCL 6-18, and K-ARS-IV
In all age groups, the mean score of CDI was 11.34 ± 7.51, which was significantly higher in females than in males (12.60 ± 8.06 vs. 9.51 ± 6.27, \( P = 0.029 \)). The mean CDI score was significantly higher in the MSAG than in the ESAG (13.28 ± 7.06 vs. 9.68 ± 7.54, \( P = 0.01 \) (Supplementary Table 2)).

The mean percentile score for internalizing problems in the K-CBCL showed no significant difference based on age group or sex. However, the mean percentile score for externalizing problems in the MSAG was significantly higher than that of the ESAG (66.92 ± 25.31 vs. 56.42 ± 26.00, \( P = 0.032 \) (Supplementary Table 2)).

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3) Correlation between PAT-Y and headache severity
In all age groups, there was no clear correlation between the frequency and intensity of headache and parenting attitudes, with only very weak, significantly negative correlations between MF and the “authoritative parenting” attitude (\( r = –0.19, P < 0.05 \)) and between VF and the “rational explanation” attitude (\( r = –0.19, P < 0.01 \) (Table 2)).
### Table 2. Correlation matrix between Parenting Attitude Test-Youth and headache severity in all age groups

<table>
<thead>
<tr>
<th>Supp exp.</th>
<th>1.00</th>
<th>Ratio expl.</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Ratio expl.</td>
<td>0.78&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00</td>
<td>Achiev pr.</td>
</tr>
<tr>
<td>Achiev pr.</td>
<td>−0.03</td>
<td>−0.09</td>
<td>1.00</td>
</tr>
<tr>
<td>High invol.</td>
<td>−0.26&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−0.29&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.41&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Punishment</td>
<td>−0.29&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−0.27&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.30&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Superintendence</td>
<td>0.52&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.35&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.17</td>
</tr>
<tr>
<td>High expect.</td>
<td>−0.30&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−0.20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.38&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Inconsequence</td>
<td>−0.27&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−0.25&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.20&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Authoritative</td>
<td>0.94&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.95&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−0.06</td>
</tr>
<tr>
<td>Authoritarian</td>
<td>−0.08</td>
<td>−0.14</td>
<td>0.38&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Permissive</td>
<td>0.01</td>
<td>−0.04</td>
<td>0.08</td>
</tr>
<tr>
<td>Neglectful</td>
<td>−0.02</td>
<td>−0.08</td>
<td>0.00</td>
</tr>
<tr>
<td>VAS</td>
<td>0.06</td>
<td>−0.04</td>
<td>−0.11</td>
</tr>
<tr>
<td>MF</td>
<td>−0.18</td>
<td>−0.17</td>
<td>0.13</td>
</tr>
<tr>
<td>VF</td>
<td>−0.15</td>
<td>−0.19&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.04</td>
</tr>
<tr>
<td>Age</td>
<td>−0.10</td>
<td>−0.12</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Supp exp., supportive expression; Ratio expl., rational explanation; Achiev pr., achievement press; High invol., high involvement; High expect., high expectation; VAS, visual analog scale; MF, monthly frequency; VF, VAS×MF/4.  
<sup>a</sup>P<0.05; <sup>b</sup>P<0.001.

### Table 3. Correlation matrix between Parenting Attitude Test-Youth and headache severity in the elementary-school age group

<table>
<thead>
<tr>
<th>Supp exp.</th>
<th>1.00</th>
<th>Ratio expl.</th>
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<tbody>
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<td>Ratio expl.</td>
<td>0.73&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00</td>
<td>Achiev pr.</td>
</tr>
<tr>
<td>Achiev pr.</td>
<td>−0.07</td>
<td>−0.13</td>
<td>1.00</td>
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<tr>
<td>High invol.</td>
<td>−0.41&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−0.49&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.51&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Punishment</td>
<td>−0.38&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−0.36&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.35&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Superintendence</td>
<td>0.47&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.21</td>
<td>0.19</td>
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<tr>
<td>High expect.</td>
<td>−0.34&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−0.20</td>
<td>0.39&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Inconsequence</td>
<td>−0.33&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−0.30&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.19</td>
</tr>
<tr>
<td>Authoritative</td>
<td>0.92&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.93&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−0.11</td>
</tr>
<tr>
<td>Authoritarian</td>
<td>−0.22</td>
<td>−0.33&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.45&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Permissive</td>
<td>0.07</td>
<td>0</td>
<td>−0.03</td>
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<tr>
<td>Neglectful</td>
<td>0.08</td>
<td>−0.06</td>
<td>−0.14</td>
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<tr>
<td>VAS</td>
<td>−0.06</td>
<td>−0.16</td>
<td>−0.28&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>MF</td>
<td>−0.06</td>
<td>−0.06</td>
<td>−0.18</td>
</tr>
<tr>
<td>VF</td>
<td>−0.09</td>
<td>−0.14</td>
<td>−0.32&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age</td>
<td>0.10</td>
<td>0.11</td>
<td>0.07</td>
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</table>

Supp exp., supportive expression; Ratio expl., rational explanation; Achiev pr., achievement press; High invol., high involvement; High expect., high expectation; VAS, visual analog scale; MF, monthly frequency; VF, VAS×MF/4.  
<sup>a</sup>P<0.05; <sup>b</sup>P<0.001.

(r = −0.26, P < 0.05), and “high expectation” (r = −0.29, P < 0.05) (Table 3).

In the MSAG, age showed a weak positive correlation with “superintendence” (r = 0.34, P < 0.05), and MF and VF showed moderate positive correlations with “achievement press” (r = 0.48, P < 0.01 and r = 0.48, P < 0.01, respectively). VF also showed a weak positive correlation with the “neglectful” attitude (r = 0.31, P < 0.05) (Table 4).

4) Correlation between other behavioral scales and headache severity

In all age groups, there was no clear correlation between the fre-
Table 4. Correlation matrix between Parenting Attitude Test-Youth and headache severity in the middle-school age group

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<td>Ratio expl.</td>
<td>0.82&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>1.00</td>
<td>Achiev pr.</td>
<td>0.04</td>
<td>–0.01</td>
<td>1.00</td>
<td>High invol.</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Achiev pr.</td>
<td>0.04</td>
<td>–0.01</td>
<td>1.00</td>
<td></td>
<td>High invol.</td>
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<tr>
<td>High invol.</td>
<td>–0.02</td>
<td>0.02</td>
<td>0.26</td>
<td>1.00</td>
<td>Punishment</td>
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</tr>
<tr>
<td>Punishment</td>
<td>–0.15</td>
<td>–0.11</td>
<td>0.22</td>
<td>0.44&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00</td>
<td>Superintendence</td>
<td></td>
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<tr>
<td>Superintendence</td>
<td>0.60&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.53&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.15</td>
<td>0.36&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.14</td>
<td>1.00</td>
<td>High expect.</td>
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<tr>
<td>High expect.</td>
<td>–0.16</td>
<td>–0.11</td>
<td>0.36&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.38&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.55&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.14</td>
<td>1.00</td>
<td>Inconsequence</td>
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<td>Inconsequence</td>
<td>–0.17</td>
<td>–0.16</td>
<td>0.22</td>
<td>0.58&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.51&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.19</td>
<td>0.29&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>0.95&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.02</td>
<td>0.00</td>
<td>–0.13</td>
<td>0.59&lt;sup&gt;b&lt;/sup&gt;</td>
<td>–0.14</td>
<td>–0.18</td>
<td>1.00</td>
<td>Authoritarian</td>
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<td></td>
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<td>0.82&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Neglectful</td>
<td>VAS</td>
<td>MF</td>
<td>VF</td>
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<td>–0.12</td>
<td>0.24</td>
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<td>0.06</td>
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<td>0.20</td>
<td>1.00 MF</td>
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<td>MF</td>
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<td>–0.04</td>
<td>–0.09</td>
<td>0.08</td>
<td>0.10</td>
<td>–0.25</td>
<td>0.05</td>
<td>0.24</td>
<td>0.22</td>
<td>–0.16 VF</td>
<td>1.00 VF</td>
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<tr>
<td>VF</td>
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<td>–0.19</td>
<td>0.48&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.18</td>
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<td>–0.08</td>
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<td>0.90&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>0.08</td>
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<td>0.23</td>
<td>0.11</td>
<td>0.00</td>
<td>–0.10</td>
<td>0.22</td>
<td>0.17</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Supp exp., supportive expression; Ratio expl., rational explanation; Achiev pr., achievement press; High invol., high involvement; High expect., high expectation; VAS, visual analog scale; MF, monthly frequency; VF, VAS×MF/4.<br/>
<sup>a</sup>P<0.05; <sup>b</sup>P<0.001.

Frequency and intensity of headache and other behavioral scales, with only very weak, significantly positive correlations between MF and VF and the internalizing problem score of the K-CBCL (r = 0.20, P < 0.05 and r = 0.21, P < 0.05, respectively) (Supplementary Table 3).

In the analysis of MSAG, MF showed weak positive correlations with the CDI score (r = 0.29, P < 0.05) and internalizing problems (r = 0.31, P < 0.05), and VF showed a weak positive correlation with the internalizing problems (r = 0.34, P < 0.05) (Supplementary Table 4). However, in the ESAG, the frequency and intensity of headaches did not show significant correlations with other behavioral scales (Supplementary Table 5).

**Discussion**

In the present study, parenting attitudes perceived by youth differed between the ESAG and MSAG. Some parenting attitudes presented different relationships with the degree of headache by age group. In the ESAG, the headache intensity presented by VAS was negatively correlated with “achievement press” and “high expectation,” and the general severity score presented by VF was negatively correlated with “achievement press,” “punishment,” and “high expectation.” In the MSAG, the headache frequency measured by MF and the general severity score showed moderately positive correlations with “achievement press,” and VF showed a weakly positive correlation with the “neglectful” attitude.

Parenting attitudes refer to all attitudes and behaviors consistently displayed by primary caregivers regarding the desired growth and development of a child when raising a child. A desirable parenting attitude is to help children take responsibility for their own lives and have the ability to control their own behavior. It also helps to form good interpersonal relationships as they grow up and to develop self-esteem [13].

Although the importance of parental roles and parenting attitudes in managing headaches in children and adolescents has been emphasized, there are not many studies on parenting attitudes based on the patient’s perspective [14-17]. In previous studies on migraine patients, migraine was positively associated with anxiety symptoms, and parents of children with chronic migraine showed higher oppressive-authoritarian attitudes than those of other headache patients [14]. In addition, another study showed that parents of children with headaches were more sensitive to health problems and showed an overprotective attitude [15]. Higher age was associated with a negative parenting style [14,16,17].

To evaluate parenting attitudes, this study used the PAT-Y developed by Lim et al. [13]. It consists of eight primary subscales and four newly developed secondary subscales. The eight primary subscales include the verified attitudes of parenting. “Supportive expression” evaluates the degree of expression of affection by parents (the ideal range is around the 75th ± 10th percentile). “Rational explanation” quantifies the degree of effort that parents make to explain their children’s mistakes so that they could understand...
them from the child’s point of view when they rebuke them (the ideal range is the 75th ± 10th percentile). “Achievement press” assesses the degree to which parents strongly demand social success from their children (the ideal range is the 60th ± 10th percentile). “High involvement” evaluates the degree to which parents are reluctant to respect their children’s privacy (the ideal range is the 50th ± 10th percentile). “Punishment” assesses the degree to which parents impose physical punishment or psychological threats on their children (the ideal range is the 40th ± 10th percentile). “Superintendence” quantifies the degree to which parents check their children’s schedule (the ideal range is the 30th ± 10th percentile). “High expectation” evaluates the degree of parents’ implicit expectations (the ideal range is the 20th ± 10th percentile). “Inconsequence” assesses the degree of inconsistency in the standards of rebuke for their children’s behavior (the ideal range is the 10th ± 10th percentile) [13].

In the present study, the range of mean percentiles of all patients for each of the eight subscales was generally in the middle of the scores (range, 46.22 to 60.46). However, there were differences according to the subscales. In general, the “supportive expression,” “rational explanation,” and “achievement press” scores were lower than the ideal ranges, and the “high expectation” and “inconsequence” scores were higher than the ideal ranges. The “high involvement,” “punishment,” and “superintendence” scores were in ranges similar to or slightly different from the ideal scores. The average scores of some attitudes did not meet the ideal ranges. Since it is often found that parental attitudes do not meet the ideal criteria in the general population [13], it is difficult to determine whether these results are characteristic of the families of headache patients.

‘Supportive expression’ perceived by patients was significantly lower in females than in males, especially in the ESAG. The reason why elementary-school girls perceived that they received less support from their parents is not clear. However, we suggest that parents of girls of this age group should express more support. The mean percentile score of “rational explanations” was significantly lower in the MSAG than in the ESAG. Parents need to increase their rational explanations in a way that adolescents can understand. The mean percentile score of “achievement press” was significantly higher in males than in females in the MSAG. This suggests that adolescent boys with headaches included in this study perceived more stress than girls by their parents because of schoolwork. However, the mean percentile scores of “achievement press” were lower than the recommended range of approximately the 60th percentile in these patients. As opposed to “rational expression,” the mean percentile scores of “high expectation” perceived by patients were significantly higher in the MSAG than in the ESAG. The mean percentile of “high expectation” for adolescents was twice as high as the recommended range. Adolescents’ perceptions that they are not meeting their parents’ expectations can be a factor that lowers their self-esteem.

Four secondary subscales were newly developed by the authors for further analysis. The authoritative attitude was defined as the average of the “supportive expression” and “rational explanation” attitudes, which are usually positive attitudes. The percentile score of the authoritative attitude was significantly higher in the ESAG than in the MSAG. The authoritarian attitude was defined as the average of four subscales (“high involvement,” “punishment,” “superintendence,” and “inconsequence”). The permissive attitude was defined as 100−(the average of the percentile scores of “achievement press” and “high expectation”). The neglectful attitude was defined as 100−(the average of four subscales: “supportive expression,” “rational explanation,” “high involvement,” and “superintendence”). There were differences by age and sex in the authoritarian, permissive, and neglectful attitudes.

As in previous studies, no clear association between headache severity and parenting attitudes was found in all age groups, including both the ESAG and MSAG [14]. However, when analyzing correlations by age group, differences were found in the correlations for several parenting attitude items. In the ESAG, the intensity and frequency of headaches were lower when the scores for the “achievement press,” “high expectation,” and “punishment” attitudes were higher, but these correlations were slight. “Achievement press” and “high expectation” corresponded to non-permissive parenting attitudes, and the “punishment” attitude corresponded to authoritarian parenting. Although it is difficult to accurately interpret these correlations, it may be possible that the attitude of parents who do not accept pampering of their child may affect their child’s expression of headaches. Whether authoritarian control is effective in reducing headache symptoms in the ESAG needs to be assessed in future studies. On the contrary, higher levels of non-permissive parenting, as exemplified by the “achievement press” and “neglectful” attitudes, were related to headache severity in the MSAG. This implies that during adolescence, parental pressure to study may increase pain, while indifference from parents may also increase the severity of headaches. Although these results should be interpreted carefully and also need further studies for validation, they imply that different parenting attitudes are related to the exacerbation of headaches in childhood and adolescence.

The use of self-reported questionnaires in evaluating parents’ parenting attitudes may have limitations in accuracy. However, parenting attitudes as scored by children may be more closely related to the behavioral characteristics of children than to the parenting attitudes of the parents [26]. A strength of the present study is that
this was the first study in Korea to assess and analyze parenting attitudes in migraine patients by age group. The limitations are that this is a retrospective study and could not be compared with controls or patients with other types of primary headaches.

Therefore, the importance of parenting attitudes in managing pain should be emphasized more strongly. Performing psychological and behavioral evaluations in the treatment of pediatric headaches would be helpful in establishing a comprehensive treatment plan for patients. The same parenting attitude may have different effects on children depending on their age. Adjusting the parenting attitude of parents according to the growth stage of their children will help to cope with headaches in these children.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.26815/acn.2022.00164.

Conflicts of interest

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

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Author contribution

Conceptualization: JHM. Data curation: KML and MSK. Formal analysis: SR. Methodology: HL and JHM. Writing-original draft: KML. Writing-review & editing: YJK and JHM.

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References


Clinical Spectrum and Treatment Outcomes of Patients with Developmental and/or Epileptic Encephalopathy with Spike-and-Wave Activation in Sleep

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Purpose: Developmental and/or epileptic encephalopathy with spike-and-wave activation in sleep (D/EE-SWAS) is a spectrum of conditions characterized by various phenotypes of cognitive, linguistic, and behavioral regression associated with spike-and-wave activation in sleep. We aimed to investigate the phenotypic spectrum and treatment outcomes of pediatric patients with D/EE-SWAS.

Methods: We retrospectively analyzed the medical records of pediatric patients diagnosed with D/EE-SWAS and treated at Severance Children’s Hospital from 2006 to 2022. We extracted information from their medical records on electroencephalography before and after treatment, types of treatment, seizure frequency, and developmental profiles. The primary outcome was reduction of the spike-wave index on electroencephalography after treatment.

Results: Twenty-one patients with a median age of 5.3 years (interquartile range, 4.1 to 6.6) at diagnosis were included. Ten patients had delayed development. The patients received various anti-seizure medications. Fourteen received long-term, high-dose steroid therapy, 10 were placed on a ketogenic diet, four received intravenous steroid pulse therapy, and one each was treated with intravenous immunoglobulin and cannabidiol. The most effective treatments were steroid therapy and a ketogenic diet, which were also effective in reducing seizures and improving cognition. Side effects during treatment were transient and treatable.

Conclusion: We described the clinical spectrum of pediatric patients with D/EE-SWAS. Steroid therapy and a ketogenic diet can be considered effective therapeutic options for patients with D/EE SWAS.

Keywords: Epilepsy; Pediatrics; Electroencephalography; Steroids; Diet, ketogenic
Introduction

Developmental and/or epileptic encephalopathy with spike-and-wave activation in sleep (D/EE-SWAS) is a spectrum of conditions characterized by cognitive, linguistic, and behavioral regression associated with marked spike-and-wave activation in sleep, which has been newly defined by the International League Against Epilepsy (ILAE) in 2022. This syndrome includes Landau-Kleffner syndrome (LKS) as a subtype and has been proposed to replace what was formerly named epileptic encephalopathy with continuous spike-and-wave in sleep (CSWS) and atypical benign focal epilepsy of childhood [1].

Electrical status epilepticus in sleep (ESES), an electroencephalography (EEG) pattern of D/EE-SWAS, has no gold-standard treatment and is often resistant to traditional anti-seizure medications [2-4]. ESES is characterized by non-rapid eye movement sleep-induced continuous spike and/or slow waves with a frequency of 1.5 to 3.0 Hz, causing neurocognitive deficits [5]. ESES is originally defined by a spike-wave index (SWI) of at least 85% of epileptiform activity during a particular period [6]. However, some studies have included an SWI in the range of 50% to 85% in the definition of ESES [4]. The clinical presentation of D/EE-SWAS varies, including developmental delay or regression, various cognitive deficits such as acquired aphasia, and seizures [6,7]. The age of incidence of D/EE-SWAS ranges from 1 to 14 years, with a peak at 4 to 8 years [1,4]. Severe neurocognitive regression is found at 5 to 6 years [7]. Early detection and intervention are important to address cognitive sequelae that could become permanent [8]. While the pathogenesis of ESES is still unknown, the cortico-thalamic circuitry is strongly suggested to be linked to the epileptiform discharges [7,9]. Moreover, there are some underlying variants in genes such as glutamate ionotropic receptor NMDA type subunit 2A (GRIN2A) that cause ESES [10].

It is difficult to establish a treatment strategy for D/EE-SWAS because there is no accepted first line of treatment, such as anti-seizure medications, immune-modulating therapy, ketogenic diet, or surgery [11,12]. Corticosteroids and adrenocorticotropic hormone are known to be effective in improving cognitive function and reducing the SWI [4,8]. A study on D/EE-SWAS showed that 26 of 37 (70%) children who received steroid therapy had improvement in seizures, and 24 of 36 (67%) patients had cognitive improvement [6]. Another study in 2020 revealed that seven of 10 (70%) CSWS patients had more than 50% seizure reduction with methylprednisolone pulse therapy [13].

This study aimed to investigate the clinical characteristics of pediatric patients diagnosed with D/EE-SWAS. In addition, we evaluated the outcomes of various treatments such as anti-seizure medicines, steroid therapy, and a ketogenic diet.

Materials and Methods

1. Study population

This retrospective study was performed at the epilepsy clinic of Severance Children’s Hospital from 2006 to 2022; patients under the age of 18 years diagnosed with D/EE-SWAS were included in the study. The inclusion criteria were as follows: (1) diagnosis of D/EE-SWAS and (2) treatment at Severance Children’s Hospital for at least 3 months. The exclusion criteria were as follows: (1) inability to undergo EEG during sleep and (2) SWI < 50% on EEG.

This study was approved by the Institutional Review Board of Severance Hospital (IRB 4-2020-0368). The requirement for informed consent was waived because of the retrospective nature of the study.

2. Data collection

We retrospectively reviewed the patients’ medical records and collected data on the age at D/EE-SWAS diagnosis, age of seizure onset, seizure type, seizure frequency before and after treatment, presence of an underlying disease, findings of brain magnetic resonance imaging (MRI), EEG findings, developmental profiles, treatments (including anti-seizure medications, a ketogenic diet, steroids, and intravenous immunoglobulin [IVIG]), and adverse effects.

We evaluated the EEG findings before and 3 months after each treatment. We performed EEG for 4 hours and ensured that more than 1 hour of sleep state was included in this period. EEGs that did not include over 1 hour of sleep were excluded from the evaluation. In addition, we evaluated the frequency of seizures 1 month before treatment and 3 months after treatment. In order to identify the type and frequency of seizures, guardians were asked to record a seizure diary, and the type and frequency of seizures mentioned in the diary were confirmed at each outpatient clinic visit. Reduction in the frequency of seizures after treatment was evaluated based on the seizure diary. Side effects were also assessed and recorded by guardians while writing the seizure diary. A developmental assessment before the treatment was conducted using questionnaires from an intelligence quotient (IQ) test, and patients were divided into three groups: moderate to severe, mild, and normal. Mild delayed development was determined when the IQ was 70 to 85 or there were two or more domains that were marked “need for follow-up” in the Korean Developmental Screening Test for Infants and Children (K-DST), and moderate to severe delayed development defined as an IQ was less than 70 or two or more domains that were in the “recommendation for further evaluation” category in the K-DST [14]. Two IQ tests were used in this study:

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the Korean Wechsler Primary and Preschool Scale Intelligence IV (K-WPPSI-IV) for ages between 2.5 and 6 years, and the Korean Wechsler Intelligence Scale for Children (K-WISC-IV) for ages between 6 and 16.9 years.

3. Treatment and outcome assessments

Various traditional anti-seizure medications were administered to patients with D/EE-SWAS. We evaluated the EEG findings and seizure frequency after 3 months of treatment. However, cases in which two or more treatments were administered within 3 months were excluded from the evaluation. All patients were previously on anti-seizure medications, and additional treatment was applied.

Patients who underwent dietary therapy were treated by pediatric epileptologists according to the classic 4:1 or 3:1 ketogenic diet or a modified Atkins diet schedule [15]. Long-term, high-dose steroid therapy was administered according to the schedule presented in our previous paper on Lennox-Gastaut syndrome [16]. During the first 2 weeks of oral prednisolone therapy, 60 mg/day was administered in four divided doses, followed by the same dose of prednisolone on alternate days for 3 months. Intravenous steroid pulse therapy was administered to patients for 3 days at a dose of 30 mg/kg per day (maximum dose, 1 g). IVIG was administered to patients at a dose of 1 g/kg per day for 2 days. Cannabidiol was administered to patients at a dose of 10 mg/kg per day after titration [17].

The primary outcome was the reduction of the SWI on EEG after each treatment. We determined that there was a response to treatment if the SWI value decreased by more than 50% from the pre-treatment value after 3 months of treatment. Additionally, we assessed the reduction in seizure frequency after treatment for patients with seizures. We evaluated treatment as effective when the seizure frequency before treatment was reduced by more than 50%. Changes in development after treatment were evaluated through interviews with guardians in the outpatient clinic. We defined a recurrence as an increase in the SWI by more than 50%.

4. Statistical analysis

Variables with a normal distribution are represented as mean and standard deviation, and variables without normal distribution are represented as medians and interquartile ranges. Data were analyzed using MedCalc version 19.2 (MedCalc Software bvba, Ostend, Belgium).

Table 1. Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>14 (66.7)</td>
</tr>
<tr>
<td>Age at diagnosis (yr)</td>
<td>5.3 (4.1–6.6)</td>
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<td>Seizure type</td>
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<tr>
<td>Focal impaired awareness</td>
<td>12 (57.1)</td>
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<tr>
<td>Generalized tonic-clonic</td>
<td>9 (42.9)</td>
</tr>
<tr>
<td>Age at seizure onset (yr)</td>
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<tr>
<td>Development</td>
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</tr>
<tr>
<td>Normal</td>
<td>11 (52.3)</td>
</tr>
<tr>
<td>Delayed</td>
<td>10 (47.6)</td>
</tr>
<tr>
<td>Mild</td>
<td>4/10 (40.0)</td>
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<tr>
<td>Moderate to severe</td>
<td>6/10 (60.0)</td>
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<td>Age at developmental delay onset (yr)a</td>
<td>2.8 (1.0–4.5)</td>
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<tr>
<td>Brain MRI</td>
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</tr>
<tr>
<td>Normal</td>
<td>17 (81.0)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>4 (19.0)</td>
</tr>
<tr>
<td>Pathogenic variant in diagnostic exome sequencing</td>
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</tr>
<tr>
<td>Underlying disease</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>20 (95.2)</td>
</tr>
<tr>
<td>Neonatal cerebral hemorrhage</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Number of treatments to each patient</td>
<td>4.2 (3.0–5.0)</td>
</tr>
</tbody>
</table>

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

aRefers to the age subjectively reported by the guardian; bThe number of treatments was the summation of different types of anti-seizure medications that had been taken during the treatment years.

Results

1. Baseline characteristics

From July 2006 to May 2022, 25 patients were diagnosed with D/EE-SWAS at Severance Children’s Hospital. However, four patients whose EEGs changed to a typical EEG pattern of Lennox-Gastaut syndrome were excluded. Finally, a total of 21 patients were included in this study.

The median age at diagnosis of D/EE-SWAS was 5.3 years (interquartile range, 4.1 to 6.6) and 14 patients (66.7%) were male. In this study, all patients experienced seizures, and the most common type of seizure was focal impaired awareness type (57.1%). Clinical seizure was detected at a median age of 3.7 years (interquartile range, 2.9 to 4.2). One patient showed clinical seizures at the age of 1 month due to a neonatal cerebral hemorrhagic lesion. His EEG findings changed to D/EE-SWAS when he was 3 years old. There were 10 patients with developmental delay, and their developmental delay was recognized by guardians at a median age of 2.8 years (interquartile range, 1.0 to 4.5). Brain MRI results revealed abnormal findings in four patients, including two cases of a mild decrease in hippocampal volume, atrophic changes in the corpus callosum, and chronic hemorrhagic lesions in the thalamus. Diagnostic exome sequencing was performed in 16 of 21 (76.2%) patients, and none of them demonstrated pathogenic variants. The median number of treatments administered to each patient was 4.2 (inter-
quartile range, 3.0 to 5.0), including steroid therapy and a ketogenic diet (Table 1).

2. Effect of each treatment on EEG, seizure, and cognitive improvements

We evaluated the effectiveness of each treatment after 3 months. Each patient had kept the previous anti-seizure medications and received new medication simultaneously. Hence, the efficacy of each treatment was assessed 3 months after each treatment started. Patients were treated with various anti-seizure drugs, long-term, high-dose steroids (66.7%), a ketogenic diet (47.6%), intravenous steroid pulse therapy (19.0%), IVIG (4.8%), and cannabidiol (4.8%). None of the patients underwent epileptic surgery. Most patients (16/21, 76.1%) received valproic acid, and 62.5% demonstrated improvements in EEG and cognitive function. Among patients who were treated with anti-seizure medications, valproic acid showed the most favorable effects (Table 2). However, approximately 70% of patients for whom anti-seizure medications were effective did not maintain the treatment effect for a year, and therefore, other treatments were administered.

The most effective therapy for EEG improvement was intravenous steroid pulse therapy (3/4, 75.0%). For seizure improvement, intravenous steroid pulse therapy (3/4, 75.0%) yielded the most successful results, followed by long-term, high-dose steroid therapy (10/14, 71.4%). In a previous study, out of 575 cases of ESES patients, high-dose steroid therapy was the second most effective treatment, with 81% (134 of 161) of patients showing improvement, after surgery, which had a 90% improvement rate (56 of 62 patients) [4]. In our study, long-term, high-dose steroid therapy was administered to 14 patients (66.7%); among them, the EEGs of 10 patients (71.4%) showed improvement. Treatment with a 3:1 ketogenic diet was provided to six patients, while two received a 2:1 ketogenic diet and two received a modified Atkins diet. The ketogenic diet had the most favorable effect on cognitive performance (8/10, 80.0%). In addition, the ketogenic diet showed favorable effects on improving EEG and reducing seizure frequency. Approximately 70% of patients who were treated with steroids and a ketogenic diet maintained the therapeutic effect for more than a year. IVIG and cannabidiol were each administered to one patient with intractable epilepsy. Cannabidiol was effective in improving EEG activity. However, this was not observed in the patients treated with IVIG.

Most patients treated with steroid therapy and a ketogenic diet showed more than a 50% reduction in the SWI. The patient presented in Fig. 1 underwent treatment with a long-term, high-dose steroid protocol. This patient not only showed an improvement in the SWI on EEG after 3 months but also demonstrated a dramatic effect on EEG after 6 months of treatment.

Table 2. Effect of each treatment on EEG, seizure, and cognitive function

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total (n=21)</th>
<th>EEG improvement</th>
<th>Seizure improvement</th>
<th>Cognitive improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-seizure medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPA</td>
<td>16 (76.1)</td>
<td>10 (62.5)</td>
<td>9 (56.3)</td>
<td>10 (62.5)</td>
</tr>
<tr>
<td>LEV</td>
<td>12 (57.1)</td>
<td>5 (41.7)</td>
<td>4 (33.3)</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>TPM</td>
<td>4 (19.0)</td>
<td>1 (25.0)</td>
<td>2 (50.0)</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>CLB</td>
<td>4 (19.0)</td>
<td>2 (50.0)</td>
<td>2 (50.0)</td>
<td>0</td>
</tr>
<tr>
<td>ZNS</td>
<td>2 (9.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LCM</td>
<td>1 (4.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LMT</td>
<td>1 (4.8)</td>
<td>1 (100.0)</td>
<td>1 (100.0)</td>
<td>1 (100.0)</td>
</tr>
<tr>
<td>PRP</td>
<td>1 (4.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CBZ</td>
<td>1 (4.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>VGB</td>
<td>1 (4.8)</td>
<td>1 (100.0)</td>
<td>1 (100.0)</td>
<td>0</td>
</tr>
<tr>
<td>PB</td>
<td>1 (4.8)</td>
<td>1 (100.0)</td>
<td>1 (100.0)</td>
<td>1 (100.0)</td>
</tr>
<tr>
<td>Long-term, high-dose steroid</td>
<td>14 (66.7)</td>
<td>10 (71.4)</td>
<td>10 (71.4)</td>
<td>8 (57.1)</td>
</tr>
<tr>
<td>Ketogenic diet</td>
<td>10 (47.6)</td>
<td>7 (70.0)</td>
<td>7 (70.0)</td>
<td>8 (80.0)</td>
</tr>
<tr>
<td>Intravenous steroid pulse</td>
<td>4 (19.0)</td>
<td>3 (75.0)</td>
<td>3 (75.0)</td>
<td>3 (75.0)</td>
</tr>
<tr>
<td>IVIG</td>
<td>1 (4.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cannabidiol</td>
<td>1 (4.8)</td>
<td>1 (100.0)</td>
<td>NA*</td>
<td>1 (100.0)</td>
</tr>
</tbody>
</table>

Values are presented as number (%). Several treatments were applied to one patient. Improvement in EEG was defined as a more than 50% reduction of the spike-wave index.

EEG, electroencephalography; VPA, valproic acid; LEV, levetiracetam; TPM, topiramate; CLB, clobazam; ZNS, zonisamide; LCM, lacosamide; LMT, lamotrigine; PRP, perampanel; CBZ, carbamazepine; VGB, vigabatrin; PB, phenobarbital; IVIG, intravenous immunoglobulin; NA, not available.

*Before the patient took cannabidiol, there were no clinical seizures.
Fig. 1. Electroencephalography (EEG) of patient who responded favorably to long-term, high-dose steroid therapy. (A) EEG before steroid therapy. (B) EEG after 3 months of steroid therapy. (C) EEG after 6 months of steroid therapy. A 9-year-old female patient whose disease was intractable with three anti-seizure medications (phenobarbital, valproic acid, and topiramate) received long-term, high-dose steroid therapy for 3 months.
Cognitive improvement was evaluated by a comparison of the findings of the K-WPPSI-IV or K-WISC-IV upon diagnosis with subsequent results from the same tests (13/21, 62.9%). The other patients, who were not tested using the K-WPPSI or K-WISC, were evaluated using the K-DST or based on the guardians’ report. Any improvement was counted, and valproate acid presented the most favorable results, with an improvement rate of 62.5% (10 of 16), except for cannabidiol, which had a 100% improvement rate (one of one).

3. Adverse effects of treatments
Steroid therapy, including long-term, high-dose steroid therapy, and intravenous steroid pulse therapy, showed various side effects in almost all patients. The most common symptoms were weight gain and Cushingoid face. However, most side effects of the steroids were treatable and transient. Among 18 patients, there were no severe side effects such as gross gastrointestinal bleeding, osteoporosis, or cardiovascular effects.

A ketogenic diet was given to 14 patients. However, only 10 patients maintained the ketogenic diet for more than 3 months. The most common side effects of the ketogenic diet were mainly gastrointestinal symptoms, and most of these adverse effects were treatable. Severe metabolic acidosis was treated while controlling the dietary ratio, and there were no life-threatening side effects (Table 3).

In addition, several patients reported side effects of anti-seizure medications, especially levetiracetam (4/12, 33.3%) and valproic acid (3/16, 18.8%), displaying aggressive behavior or an increase in seizure frequency. Two patients who received clobazam (50%) showed lethargy and general weakness. The single patient who received cannabidiol complained of mild abdominal pain.

### Table 3. Side effects of patients with steroid therapy and a ketogenic diet

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid therapy*</td>
<td>18</td>
</tr>
<tr>
<td>Cushing face</td>
<td>18 (100)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>18 (100)</td>
</tr>
<tr>
<td>Irritability</td>
<td>12 (66.7)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Ketogenic diet</td>
<td>10</td>
</tr>
<tr>
<td>Lethargy</td>
<td>4 (40.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (30.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (20.0)</td>
</tr>
<tr>
<td>Severe metabolic acidosis</td>
<td>2 (20.0)</td>
</tr>
</tbody>
</table>

*Values are presented as number (%).

*Steroid therapy includes long-term, high-dose steroid therapy, and intravenous steroid pulse therapy.

**Discussion**

This study described the clinical characteristics of D/EE-SWAS and evaluated the various treatments employed in its management. The global incidence of D/EE-SWAS is 0.6% to 0.7% of all childhood epilepsies [1]. The exact incidence of D/EE-SWAS in South Korea, is not known. According to the Health Insurance Review & Assessment Service of South Korea, 27 patients with LKS had EEGs showing the ESES pattern and were under medical care in 2019. We can assume that the incidence of D/EE-SWAS is extremely low in South Korea compared to the prevalence of LKS in Japan in 2014, which was 1 in a million in patients aged 5 to 14 years [18].

In this study, the median age of seizure onset in D/EE-SWAS patients was 3.7 years (interquartile range, 2.9 to 4.2), which is similar to that in other studies in which the seizure onset peaked at the age of 4 to 5 years [1]. While the onset of seizures in patients occurred at a median age of 3.7 years, the onset of developmental delay was approximately a year ahead, at a median age of 2.8 years. This suggests that developmental delays could be the early sign of D/EE-SWAS. Other studies have reported that the cause of D/EE-SWAS could be variants in genes such as GRIN2A and structural anomalies of the brain [19,20]. However, our study did not detect any specific pathogenic gene variants or structural anomalies.

While valproate showed a response in nine of 51 (17.6%) CSWS patients in another study in 2021 [6], our study population demonstrated a good response on EEG for nine of 21 (56.3%) patients. However, maintaining the therapeutic effects of anti-seizure medications was a major concern [4]. In Germany, acetazolamide was the most widely used drug, in 96 of 345 patients, resulting in EEG improvements in 22 of 96 (22.9%) patients [6].

In this study, steroid therapy and a ketogenic diet were the key components in lowering the SWI, whereas six recent studies showed variable results of ketogenic diets on ESES [21]. Many other studies have also revealed that steroid therapy yields good outcomes in terms of EEG results and cognitive improvement. There is no standard steroid therapy in terms of steroid type, dose, and treatment duration. In France, among 44 patients with CSWS, including four LKS patients on prednisolone, a favorable response was found in 34 (77.2%) patients; 22 of 44 patients showed improvements on EEG, better development, and shorter SWI duration [22]. A study in China, with 82 ESES patients, including six
LKS patients, showed that 68 of 82 (82.9%) ESES patients and six of six (100%) LKS patients had significantly lower SWI after receiving prednisolone (1 to 2 mg/kg/day) for 6 months [23]. However, in another Chinese study, 1-year recurrence was observed in 42 of 82 (51%) ESES patients and three of six (50%) LKS patients. Our study showed a low recurrence rate (approximately 30%) with steroid therapy and a ketogenic diet. Early diagnosis and treatment, with quicker normalization of EEG, could minimize neurocognitive deterioration in patients with CSWS.

The mechanism of corticosteroid therapy in refractory epilepsy remains unclear, although several hypotheses have been proposed. By modulating gamma-aminobutyric acid receptors, steroids reduce the excitability of neurons, thus acting as anti-seizure medications. Other receptors such as glycine, nicotinic acetylcholine, and 5-hydroxytryptamine 3 (5-HT3) receptors, are also known as target-modulating receptors of steroids [24]. A ketogenic diet is known to have numerous mechanisms that together reduce neuronal excitability [25]. For example, medium-chain fatty acids have their own independent anti-epileptic effects, and decanoic acid can act as an anti-seizure medication by directly inhibiting a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors.

This study has several limitations. First, a small number of patients was included because of the low prevalence of D/EE-SWAS. Second, the developmental status was assessed using IQ or the K-DST when the patient was first diagnosed or manifested worsening of the disease. Accordingly, the patient’s cognition after 3 months of each treatment was subjectively evaluated by a caregiver’s report, and formal IQ tests were not performed every time. Further studies should use standardized rating scale such as the Clinical Global Impression or a customized questionnaire with a scale given before and after treatment. Third, since cannabidiol and IVIG treatments were received by one patient each, we were not able to properly evaluate their efficacy. Although valproate was used for the first treatment, the order of subsequent treatments was not consistent. Therefore, further research may be needed to determine the effectiveness of the treatment order.

In conclusion, this study demonstrated the characteristics and current treatments of a rare type of epilepsy, D/EE-SWAS, in South Korea. Although the hallmark of D/EE-SWAS is developmental delay, approximately half of the patients had developmental delays and cognitive dysfunction [2]. Steroid therapy and a ketogenic diet could be considered effective therapeutic options for the management of patients with D/EE-SWAS. Further studies should be conducted with larger numbers of patients to compare the efficacy of various treatments.

Conflicts of interest

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

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References

A Case of Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease with Acute Bilateral Total Blindness

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Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) is a demyelinating disease of the central nervous system. MOG is a glycoprotein located on the surface of oligodendrocytes that acts as a cellular adhesive molecule in the central nervous system. The role of MOG has not been fully elucidated, but it is known to regulate microtubule stability and modulate myelin-immune interactions by mediating the complement cascade [1]. MOGAD clinically presents with optic neuritis, transverse myelitis (TM), or rarely, acute disseminated encephalomyelitis (ADEM), depending on the location of the lesion. The clinical manifestations of MOGAD differ by age. Younger children mostly present with an ADEM phenotype. In contrast, optic neuritis is commonly observed in older children and adults [2]. Since the symptoms correlate with the location of the demyelinating lesion, it is often difficult to distinguish between multiple sclerosis (MS), aquaporin-4 antibody-associated neuromyelitis optica spectrum disorder (AQP4-NMOSD), and monophasic acquired demyelinating syndrome (ADS). These demyelinating diseases were traditionally classified according to recurrence. Since the early 2000s, advances in diagnosis using antibody assays have led to the recognition of MOGAD as a new disease entity distinct from other demyelinating diseases [3]. Herein, we present a case of MOGAD with complete remission following a combination of plasmapheresis, intravenous immunoglobulin (IVIG), and steroids. This study was approved by the Institutional Review Board of the Gangnam Severance Hospital, Yonsei University College of Medicine (3-2017-0168). The requirement for informed consent for this retrospective study was waived by the board.

A 12-year-old girl complained of progressive visual loss for 3 days and became completely blind. She had a history of an upper respiratory tract infection a week prior to symptom onset. The visual defect started in the right eye and progressed to the left eye, eventually affecting both eyes. Eye examination revealed decimal visual acuity of 0.1/0.3 (right/left). A fundus examination with pupil dilation revealed a swollen optic disc in both eyes but no disc redness, retinal hemorrhage, or changes in the retinal vessels. NMOSD, ADEM, MS, and other central nervous system inflammatory diseases were considered in the differential diagnosis. The patient was treated with methylprednisolone (1 g/day) for 5 days. However, her vision did not improve, and she was referred to a tertiary hospital.

On admission, the patient's visual acuity had deteriorated to hand motion in the right eye and a
finger count of 10 cm in the left eye. Automated perimetry revealed complete depression of the visual field in both eyes. Blood tests and cerebrospinal fluid (CSF) analyses were performed, and the results were normal. The C-reactive protein level and erythrocyte sedimentation rate were normal. CSF analysis revealed normal protein levels with a slight increase in the white blood cell count and negative oligoclonal bands. Brain magnetic resonance imaging (MRI) revealed bilateral optic neuritis, including the optic nerves, optic chiasm, and focal abnormalities in the subcortical white matter and cortical gray matter of both insula (Fig. 1A and B). There was no evidence of demyelination of the spinal cord. Six cycles of plasmapheresis were initiated, followed by IVIG at 2 g/kg for 2 days.

During admission, serum MOG antibody (MOG immunoglobulin G) was tested using a fluorescence-activated cell sorting live cell assay. It tested positive, with a positive cell ratio of 0.422 (negative, ≤ 0.141; borderline, > 0.141 or ≤ 0.254; positive, > 0.254). Serum anti-aquaporin 4 antibody was negative. We were able to confirm her diagnosis as MOGAD. Ophthalmic examinations were performed on consecutive days after each cycle of plasmapheresis. The patient’s visual acuity and visual field improved progressively. After six cycles of plasmapheresis, the MOG antibody level test revealed a negative conversion. At discharge, the patient’s visual acuity improved to 0.04/0.02 (right/left), and the visual field also improved to 71%/31% (right/left). She was discharged with a prescription of oral prednisolone at 1 mg/kg/day and monthly administration of IVIG (1 g/kg) until full recovery of visual acuity.

One month after discharge, the patient visited our hospital for her monthly IVIG treatment and follow-up MRI. The brain MRI demonstrated resolution of the bilateral optic neuritis, including the optic nerves and optic chiasm, and there were no newly developed lesions on follow-up MRI (Fig. 1C and D). There was also no evidence of demyelination in the spinal cord on spinal MRI. An ophthalmic examination revealed a visual acuity of 0.08/0.06 (right/left) and a visual field of 65%/71% (right/left). Owing to the side effects of oral prednisolone, such as iatrogenic Cushing syndrome, we prescribed deflazacort to the patient instead of prednisolone and gradually tapered off. She regularly had outpatient department visits for routine check-ups. Three months after treatment, an examination revealed further improvement in visual acuity (0.9/0.8, right/left). Three cycles of monthly IVIG were administered, and the patient’s visual acuity almost returned to the pre-morbid level, with a visual field of 94%/97% (right/left) (Fig. 2). There was no recurrence during the 4-month observation period, and the patient remained seronegative for the MOG antibody.

Between 0.5 and 1.66 per 100,000 children have ADS. When children first present with ADS, the differential diagnosis is crucial because specific and timely treatment may be required [4]. MOGAD, MS, and AQP4-NMOSD are the common diagnostic possibilities. One-fifth of children with ADS are diagnosed with MS, and MOG-Ab is found in approximately 30% of children with ADS [3]. Optic neuritis and TM are the frequent symptoms in all three diseases, whereas ADEM is present in MOGAD and AQP4-NMOSD, but rarely in MS. Whereas monocular optic neuritis is common in MS, bilateral eyes are affected in MOGAD and AQP4-NMOSD. The diagnosis should be confirmed based on laboratory findings, especially an antibody assay [3].

Management of an acute demyelinating event is key to reducing inflammation and promoting recovery without sequelae. The first-line treatment involves intravenous steroids (1–2 g/day for 5–7 days). If the patient is resistant to steroids, plasma exchange or IVIG is used as second-line treatment. Considering the severity and risk of relapse, chronic immunotherapy may be needed to prevent relapse. Rituximab, azathioprine, tacrolimus, mycophenolate

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**Fig. 1.** Magnetic resonance imaging (MRI) findings. The initial axial fluid attenuated inversion recovery images revealed bilateral optic neuritis (arrows, A) and focal abnormalities in the subcortical white matter and cortical grey matter in insula (arrows, B). Follow-up MRIs revealed. Follow-up MRIs revealed resolving process of bilateral optic neuritis and resolved state of both insula lesions (C, D).
mofetil, and methotrexate are commonly used [5]. In MS, initial disease-modifying treatment is recommended for better control of clinical and radiological disease activity owing to a higher relapse rate. However, MOGAD tends to be monophasic, and the disease-modifying treatment used for MS is not suitable [6].

The clinical course of MOGAD may be monophasic or relapsing [1]. Younger children or those with the ADEM phenotype tend to have monophasic experiences, and persistent seropositive MOG antibodies may be associated with a higher relapse rate. In particular, the relapse rate is about 50% in MOG-optic neuritis (ON), and regular follow-up is needed, including ophthalmic examinations, neurologic examinations, and MOG antibody level tests [7]. The severity of relapse is variable, but most children recover quickly. Almost complete remission is usually seen [2]. The severity is also age-dependent. Symptomatic brain involvement is more likely to occur in younger children than in older children [8].

In conclusion, we present a case of MOGAD manifesting as optic neuritis that was treated with steroids, plasmapheresis, and IVIG. The patient recovered, with MOG antibody seronegativity and no relapse. A systematic review of pediatric MOGAD included 61 studies, all but one of which used corticosteroids as acute-phase treatment. However, IVIG was used in 21% (128/621) of patients and plasmapheresis was only performed in 4% (26/621) [9]. MOGAD is commonly well treated with intravenous steroids, but cases in which the patient is refractory to steroids or presents with severe symptoms such as total blindness could be managed with plasmapheresis and IVIG for a better prognosis, as observed in our case.

Conflicts of interest

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

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Author contribution

Acknowledgements

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References

A Patient with Pyridoxine-Dependent Epilepsy Who Was Treated with Triple Therapy

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Pyridoxine-dependent epilepsy (PDE) is a type of developmental and epileptic encephalopathy manifesting as seizures that are resistant to anti-seizure medication (ASM) but responsive to pharmacologic doses of pyridoxine [1]. PDE caused by bi-allelic mutations in the aldehyde dehydrogenase 7 family member A1 (ALDH7A1) gene on chromosome 5q32.2 is designated PDE-ALDH7A1 [1,2]. Mutations at this locus are associated with decreased activity of α-aminoadipic semialdehyde (α-AASA) dehydrogenase in lysine metabolism [3]. PDE-ALDH7A1 is a rare disease with an estimated incidence of 1:65,000 to 1:250,000 live births [2]. Refractory neonatal seizures are the most common presentation; however, 25% to 30% of patients were found to present with seizures outside of the neonatal period, and varying intellectual disabilities and developmental delays were found in 75% of patients [4].

We report the case of a 9-year-old boy with intractable seizures related to homozygous ALDH7A1 mutations, who improved after triple therapy. The patient had neonatal seizures on his 12th day of life. He was started on multiple ASMs, including phenobarbital, phenytoin, levetiracetam, topiramate, vigabatrin, and clonazepam; however, his seizures and the related epileptiform discharges on electroencephalography (EEG) persisted. He received empiric high-dose vitamin therapy, which included pyridoxine, inconsistently. For the next 7 years, he was admitted repeatedly for recurrent status epilepticus whenever his medications were discontinued.

When the patient was 7 years old, his father stopped giving him the prescribed vigabatrin and pyridoxine. Ten days after therapy interruption, he was admitted to the intensive care unit (ICU) for seizures, vomiting, and poor general condition. Doctors resumed vigabatrin and pyridoxine. However, the recurrence of vomiting prevented oral intake of these medications, and he had seizures again. He was readmitted to the ICU and was administered pyridoxine at 50 mg/day (2 mg/kg body weight), after which the seizures stopped.

Prompted by this clinical information, whole-exome sequencing was performed in the proband, mother, and father for an accurate diagnosis. Compound heterozygous mutations were identified in the ALDH7A1 genes: NM_001182.4:c.210C > A (p.Cys70Ter) and c.871+5G > A. The variants confirmed by Sanger sequencing were classified as pathogenic according to the guidelines of the American College of Medical Genetics and Genomics [5]. A segregation study showed both parents as carriers of the variants (Fig. 1). We diagnosed the patient with PDE and increased the pyridoxine dose to 300 mg/day (10 mg/kg). Since pyridoxine supplementation, he became sei-
Fig. 1. Findings of genetic testing of the patient. The patient and his relatives underwent genetic testing. Both copies of the patient's aldehyde dehydrogenase 7 family member A1 (ALDH7A1) gene had mutations, albeit different ones. Each of these mutations was found in his father and mother, who were asymptomatic carriers. A deceased elder brother presented similarly and is assumed to have had the mutations. An elder sister showed no clinical or genetic evidence of the disease.

Liver function and his EEG demonstrated improvement. However, there was no significant change in cognitive development and behavior. He was still apt to scream and run around. He exhibited violent behavior and was unable to obey commands. We initiated lysine restriction and prescribed a lysine-free amino-acid formula. We also added folic acid (1 mg/day) and arginine (4,000 mg/day; 120 mg/kg body weight). After only 4 months of lysine restriction, he was able to stay in his bed without the need for restraints and to obey his father's commands.

To diagnose PDE clinically, 100 to 500 mg of pyridoxine is administered intravenously [2] while monitoring the patient's EEG, oxygen saturation, and vital signs [1]. Clinical seizures generally cease within several minutes in patients with PDE [1]. Caution should be exercised in administering an intravenous infusion of pyridoxine because it could cause a sudden increase in the neurotransmitter gamma-aminobutyric acid, leading to electrocerebral silence, which manifests clinically as excessive drowsiness or coma [1].

Molecular genetic testing is the only reliable method to confirm the clinical diagnosis of PDE, to diagnose the disease prenatally, and to screen family members who may be carriers [1,2]. There are no specific seizure or EEG patterns with this disease [6]; therefore, PDE needs to be tested in any cases of epilepsy with unknown etiology [2]. Additional biochemical testing for α-AASA and Δ1-piperideine-6-carboxylate in serum, urine, and cerebrospinal fluid should be performed when a single pathogenic variant or a variant of uncertain significance is identified on genetic testing [1,2].

Triple therapy consists of pyridoxine and arginine supplementation, as well as lysine restriction, and is effective in PDE-ALDH7A1 [7]. PDE-ALDH7A1 should be treated with pyridoxine supplementation of 100 mg/day in newborns, 30 mg/kg/day (maximum of 300 mg/day) in infants, and 5 to 30 mg/kg/day (maximum of 500 mg/day) in children and adolescents [2]. All patients on pyridoxine supplementation must undergo clinical screening for peripheral neuropathy (PN) [2]. Initially, only patients treated with > 500 mg/day of pyridoxine were considered at risk for PN [8]. However, Ghavanini and Kimpinski [9] suggested that even pyridoxine doses as low as 50 mg/day, if used for greater than 6 months, may increase the risk of neuropathy. Lysine reduction therapies have been associated with improved long-term neurologic outcomes [2]. The use of a lysine-free formula with amino acid supplementation permits the limitation of lysine intake while ensuring adequate intake of the other amino acids [10]. Lysine is an essential amino acid and over-restriction of lysine could lead to malnutrition [8]. Thus, patients on a lysine-restricted diet should have plasma amino acids measured at least every 3 ( < 3 years of age) to 6 months ( > 3 years of age) [2]. Pharmacologic doses of arginine compete with lysine for intestinal absorption, transport across the blood-brain barrier, and entry into the mitochondria [2]. Previous recommendations for arginine dosing recommended 150 mg/kg/day if administered in addition to a lysine-restricted diet and 400 mg/kg/day if administered with pyridoxine alone [2]. Coughlin et al. [2] suggested that a higher dose of arginine (300 to 600 mg/kg/day in adults) may be required to impact lysine transport.

The patient had an elder brother who died of status epilepticus and sepsis (Fig. 1). This boy first had seizures at 2 months of age and was treated with ASMs and pyridoxine at 12.5 mg/day. When he was 7 years old, he was unable to take oral medications and supplements due to vomiting, and he eventually died. He did not undergo next-generation sequencing, but he is presumed to have had the ALDH7A1 mutations. Because the discontinuation of pyridoxine coincided with that of the ASMs, physicians failed to relate the seizures with the withdrawal of pyridoxine.

In summary, we report the case of a boy with intractable seizures related to ALDH7A1 mutations. Triple therapy controlled his seizures and improved his behavior. This case describing the diagnosis and treatment of PDE may be of interest to pediatricians and pediatric neurologists who manage this disease.

This study was approved by the Institutional Review Board of the Gangnam Severance Hospital, Yonsei University College of Medicine (3-2017-0168). The requirement for informed consent for this retrospective study was waived by the board.
Conflicts of interest

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

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References

A Paramyotonia Congenita Family with an R1448H Mutation in SCN4A

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Paramyotonia congenita (PC) is a type of Na⁺ channelopathy caused by mutations in the Na⁺ voltage-gated channel alpha subunit 4 (SCN4A) gene on chromosome 17q23, which encodes voltage-gated Na⁺ channels (Na⁺v1.4) in skeletal muscles and is inherited in an autosomal dominant pattern [1,2]. These channels are integral membrane proteins that exist in most excitable cells. They are mainly responsible for rapid membrane depolarization, which is the initial phase of the action potential. Rapid inactivation after an action potential prevents repetitive excitation and maintains normal physiological excitability of skeletal muscles.

Abnormal activity of human skeletal muscle due to a dysfunctional Na⁺ channel α-subunit with an SCN4A mutation causes excessive excitability and leads to the activation or inactivation of the channel. Clinical phenotypes associated with SCN4A mutations include PC, type 2 hyperkalemic periodic paralysis (PP), type 2 hypokalemic PP, congenital myasthenic syndrome-16, and acetazolamide-responsive myotonia congenita [1]. Furthermore, PC is characterized by muscular myotonia without weakness, and it mainly affects the muscles of the neck, face, and upper limbs. PC typically occurs in infancy or childhood and is triggered by exposure to cold or physical activity [3].

In this paper, we report the case of a male adolescent and his three-generation family with PC caused by an SCN4A mutation. This case was reviewed and approved by the Institutional Review Board of Pusan National University Hospital (IRB No. 2205-013-114). Informed consent was obtained from all parents. Patients’ medical records and other data were anonymized to ensure confidentiality.

The proband was a 14-year-old boy with a 2-year history of episodic muscular stiffness and weakness. The patient often experienced weakness and stiffness in the lower and upper extremities. During exercise, the lower extremities were affected more than the upper extremities; however, symptoms were also observed in the hands, arms, and face. During the asymptomatic period, the patient exercised normally. However, once symptoms developed, the patient was unable to move. When exposed to cold environments, such as when washing the face or during cold weather, symptoms were aggravated in the exposed body parts.

The patient was born at a gestational age of 40 weeks via normal vaginal delivery, weighing 3,400 g. He showed normal development and growth. The mother of the patient also had stiffening and muscle weakness in the upper extremities, face,
and lower extremities from around the age of 10, which worsened with cold exposure and exercise. The 16-year-old sister of the patient also showed similar symptoms from around the age of 9. The patient’s maternal aunt and grandmother presented similar symptoms. All laboratory tests, including complete blood count, electrolytes, liver function tests, creatine kinase level, and thyroid function tests, were normal. Electromyography performed at another hospital revealed a diffuse myotonic discharge.

We conducted diagnostic exome sequencing (DES) of the proband. Genomic DNA was extracted from peripheral blood leukocytes and DES was performed by Green Cross Genome (Yongin, Korea) using the Celenics G-Mendeliose DES panel. The panel includes 80,962 targeted exons in 5,870 genes and used DNBSEQ-G400 (MG1 Tech. Co., Shenzhen, China) with a 2 × 100 paired-end read method. The sequenced reads were mapped and compared with the published human genome build (UCSC GRCh37/hg19 reference). We identified a heterozygous missense mutation, c.4343G > A (p.R1448H) in SCN4A (Fig. 1). The p.R1448H variant in SCN4A has not been reported in population databases, such as gnomAD (https://gnomad.broadinstitute.org/) and Korean Reference Genome Database (KRGDB). In in silico predictions (sorting intolerant from tolerant [SIFT], polyphen, Mutation Taster), the SIFT score was 0 (deleterious), and the polyphen-2 score was 1 (probably damaging). We conducted Sanger sequencing for the variant in four family members, including the proband, a sister, and both parents. The variant was co-segregated with the affected members (proband, a sister, and a mother) within the family (Fig. 2).

The R1448H variant has been previously reported in PC patients and has been found to be related to the phenotype of PC in functional studies [4]. Thus, the variant was interpreted as a likely pathogenic variant according to the 2015 American College of Medical Genetics guideline [5]. We administered lamotrigine (3 to 3.5 mg/kg/day) to the patient and his sister.

The symptoms of the lower extremities improved, although intermittent dystonia in the hands and face persisted.

It has been shown that PC worsens with exposure to cold, is relieved by warm temperature, and is aggravated by continued activity (paradoxical myotonia) [1]. Symptoms are usually noticed during infancy and present in most patients as teenagers. The progression of PC with age and muscle atrophy are not observed. Symptoms can last from a few seconds to a few minutes and, in some cases, for several days. Some patients experience worsening symptoms after consuming foods that are high in potassium. Patients with PC are instructed to avoid potassium-rich foods. Although no permanent disability remains, there are limitations in activities of daily living. The treatment of PC involves avoiding sudden exposure to very cold weather and sudden intense physical activities. Potassium-rich foods can trigger muscle stiffness, and patients should know how to manage their potassium intake. Medications that block sodium channels, such as mexiletine and lamotrigine, may reduce stiffness in PC patients [2,6].

Fig. 1. Genetic analysis by Sanger sequencing of the proband and the family. The proband, sister, and mother had a heterozygous c.4343G>A (p.R1448H) mutation in Na+ voltage-gated channel alpha subunit 4 (SCN4A).
Voltage-gated Na⁺ channels are integral membrane proteins that conduct Na⁺ through cell membranes. In excitable cells, Na⁺ channels are responsible for the rising phase of action potentials, known as “depolarization.” There are many subtypes of Na⁺ channels, and Naᵥ1.4 is mainly present in skeletal muscles. The Na⁺ channels consist of large α- and accessory β-subunits. The α-subunits exhibit the core function of the channel, which conducts Na⁺ in a voltage-gated manner, even in the absence of β-subunits. The α-subunit is encoded by the SCN4A gene at chromosome 17q23.3, and the β-subunit is encoded by the SCN1B gene at chromosome 19q13.11 [7]. Mutations of SCN4A cause several subtypes of sodium channelopathies, including PC, hyperkalemic PP, hypokalemic PP, congenital myasthenic syndrome, and atypical acetazolamide-responsive myotonia congenita [1]. Mutations of SCN1B have been associated with cardiac arrhythmias, developmental epileptic encephalopathy, and generalized epilepsy with febrile seizures [7]. Naᵥ1.4 carries the majority of the inward Na⁺ current. The activation of the channel generates an action potential, and the rapid inactivation of the channel after an action potential helps the membrane potential to return to the resting potential quickly. This entire process maintains normal skeletal muscle contraction. Gain-of-function mutations in SCN4A, the gene that encodes skeletal muscle Naᵥ1.4, enhance the inward Na⁺ current, which leads to increased membrane excitability and a decrease in channel inactivation [2,8]. As a result, there is an inappropriately increased excitability of action potentials due to the increased amount of available Na⁺ channels (impaired inactivation) and the easy opening of Na⁺ channels with mild depolarization (increased excitability) from resting potential due to increased extracellular Na⁺ levels. This pathophysiological mechanism can lead to an initial burst of myotonia discharges and results in the symptom of stiffness. SCN4A mutations produce various clinically distinct skeletal muscle disorders, including hyperkalemic PP, PC, potassium-aggravated myotonia, hypokalemic PP, and congenital myasthenic syndrome. The SCN4A gene comprises several exons and is associated with various clinical phenotypes. The clinical presentation of patients varies depending on which nucleotide, codon, or amino acid changes, and the number of mutant exons. If there is enhanced excitability with a small amount of Na⁺ influx, myotonia due to increased excitability can be observed. Mutations associated with prominent inactivation defects (abundant Na⁺ influx) with disrupted slow inactivation increase the susceptibility to PP from sustained depolarization of the resting potential [9]. After the discharge level is increased, most Na⁺ channels become inactive and do not respond to stimuli, resulting in paralysis symptoms [8,9].

In conclusion, PC is very rare, with an estimated prevalence of less than 1:100,000 [10]. In Korea, there have been no previous reports of PC caused by the R1448H mutation of SCN4A, and the present case is the youngest patient with PC. It is important to obtain a detailed history, recognize the characteristic symptoms of PC, and conduct appropriate diagnostic tests. We hope that this case report will enhance pediatric neurologists’ understanding of PC.

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.
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Conceptualization: YMK. Data curation: YJL. Methodology: YHJ. Project administration: YHJ. Writing-original draft: YJL. Writing-review & editing: YMK.

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**References**

Myoclonic–Atonic Epilepsy Masquerading as Subacute Sclerosing Panencephalitis: A Clinical Conundrum

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Myoclonic epilepsy of infancy, myoclonic-atonic epilepsy (MAE) with onset in early childhood, and later-onset syndromes such as juvenile myoclonic epilepsy, eyelid myoclonic epilepsy, and myoclonic absence epilepsy are all examples of childhood-onset myoclonic epilepsy syndromes. Degenerative brain disorders, subacute sclerosing panencephalitis (SSPE), autoimmune disorders, and a few mitochondrial abnormalities are among the other uncommon causes. There have been attempts to define hereditary myoclonic epilepsies that do not meet the recognised criteria for myoclonic epilepsy syndromes [1]. The cognitive outcomes of epilepsy syndromes vary, but in general, they have a good prognosis. Myoclonic-atonic epilepsy is classified as an epileptic encephalopathy, and the cognitive outcome can be normal to severely impaired [2].

SSPE, in contrast, is a debilitating neurological illness that has so far eluded treatment. It is characterised by cognitive decline, periodic myoclonus, ataxia, vision complaints, a vegetative state, and death [3]. Clinicians usually identify SSPE using a combination of classic clinical features paired with elevated anti-measles antibody titres in the cerebrospinal fluid (CSF). Thus, a problem arises when a clinician is faced with a case of SSPE presenting in its early stages or with atypical symptoms. In the case described herein, the initial presentation suggested SSPE with an atypical presentation, but the work-up to rule out other possibilities and careful monitoring led to a final diagnosis of MAE.

A 6-year-old boy with normal development, had repeated brief generalised tonic-clonic seizures (GTCS) for the past 4 months (1 to 2 episodes/week). Valproic acid was started at 20 mg/kg/day, but discontinued 2 weeks later due to new-onset behavioural issues and transaminitis. Levetiracetam was then initiated at 20 mg/kg/day and optimised to 25 mg/kg/day. According to the mother’s account, the seizure frequency increased to 3 to 4 episodes/week. At this point, la-cosamide was started at 2 mg/kg/day and increased weekly to 4 mg/kg/day. He presented to the emergency with head drop. He had not experienced any episode of GTCS for the last one and half months. Head drop occurred more frequently in the morning. He also had progressive cognitive decline and behavioural issues such as hyperactivity, temper tantrums, irritability, and emotional lability. The child had been vaccinated against measles at 9 and 15 months of age, and had never had clinical measles. The Childhood Behaviour Checklist showed borderline scores for inattention (68) and hyperactivity (67). He
had no dysmorphism or neurocutaneous markers, and the neurological examination was essentially normal. The eye examination revealed no pigmentary, necrotising, or optic atrophy, and the hearing test was normal. Autoimmune encephalitis, SSPE, and progressive myoclonic epilepsies were the first clinical possibilities. His blood count, arterial lactate, ammonia, glucose, and ketone levels were in the normal range. Human immunodeficiency virus (HIV) serology was negative. The CSF showed two cells/mm$^3$ (lymphocytes), 15 mg/dL protein, and 61 mg/dL glucose (random blood sugar 96 mg/dL), sterile CSF culture, and a negative CSF viral panel. The measles antibody titres in serum and CSF determined by the enzyme-linked immunosorbent assay method are presented in Table 1.

The sleep electroencephalography (EEG) record showed frequent, quasi-periodic (6 to 10 seconds) generalised bursts of spike-and-wave (2.5 to 3.0 Hz, 450 to 550 μV) and polyspike discharges lasting for 0.5 to 3 seconds (Fig. 1). Activation procedures, such as photic stimulation and hyperventilation, did not yield any additional information. Brain magnetic resonance imaging (MRI) was normal. Despite the absence of classical EEG findings, SSPE still remained a possibility due to evidence of the intrathecal production of measles antibodies.

The child was further investigated for alternative treatable aetiologies. CSF titres of anti N-methyl-D-aspartate (NMDA) receptor antibody and serum antibodies against alpha-amino-3-hydroxy-5-methyl-4-isoxazole (AMPA), gamma-aminobutyric acid type A and B (GABA), contactin-associated protein-like 2 (CASPR2), glutamic acid decarboxylase (GAD) were negative. With a working diagnosis of seronegative autoimmune encephalitis, immunotherapy was planned. Pre-therapy, the CSF anti-measles antibody and CSF/serum ratio were obtained again from the same laboratory; the results were still positive, but with decreasing titres (CSF/serum ratio reference for measles IgG antibody, 7.7). A paired sample was also sent to two other laboratories because we continued to have doubts about the elevated anti-measles antibody titres. The child was administered intravenous immunoglobulin at 400 mg/kg/day for 5 days and intravenous methylprednisolone at 30 mg/kg/day for 5 days. The antiseizure medications were optimised (levetiracetam at 30 mg/kg/day, lacosamide at 6 mg/kg/day, clobazam at 0.5 mg/kg/day). The child was discharged and followed up after 4 weeks. The repeated CSF measles antibody titre was in the normal range. The child showed improvements in the behavioural and cognitive profile and the frequency of head drop decreased significantly. At this time, his parents complained of new paroxysms characterised by sudden cessation of ongoing activity along with a vacant stare lasting for 10 seconds, especially upon waking up. When he was made to hyperventilate for three minutes, an episode of absence seizure was noted. The same was captured in a video EEG recording that showed frequent generalised discharges of spike-and-wave discharges (2.5 to 3.5 Hz, 550 to 650 μV) lasting for 10 to 15 seconds with abrupt onset and offset and no accentuation of discharges on photic stimulation (Fig. 2). In view of this additional finding, we disregarded the diagnosis of SSPE and considered a possible diagnosis of MAE. The child was started on etho-

### Table 1. Serial serum and CSF IgG antibodies against measles

<table>
<thead>
<tr>
<th>Date</th>
<th>Serum total IgG (700–1,600 mg/dL)</th>
<th>CSF total IgG (0–3.4 mg/dL)</th>
<th>Serum measles virus IgG (&lt; 13.5 AU/mL)</th>
<th>CSF/serum measles IgG antibodies quotient reference by EIA (&gt; 1.5 positive)</th>
<th>Oligoclonal bands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nov. 13, 2021</td>
<td>771</td>
<td>0.31</td>
<td>121</td>
<td>33.8</td>
<td>Absent</td>
</tr>
<tr>
<td>Dec. 3, 2021</td>
<td>864</td>
<td>1.04</td>
<td>110</td>
<td>7.7</td>
<td>Absent</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; IgG, immunoglobulin G; EIA, enzyme immunoassay.

**Fig. 1.** (A) An electroencephalography (EEG) longitudinal bipolar montage (sweep, 30 mm/sec; sensitivity, 150 μV/cm; bandpass, 1.6 to 70 Hz) shows interictal generalised bursts of spike-and-wave (2.5 to 3.0 Hz/450 to 550 μV) and polyspike discharges. (B) An EEG longitudinal bipolar montage (sweep, 10 mm/sec; sensitivity, 150 μV/cm; bandpass, 1.6 to 70 Hz) shows interictal generalised bursts of spike and polyspike discharges with variable periodicity (6 to 10 seconds), with each burst lasting for 0.5 to 3 seconds.
suximide (20 mg/kg/day) and continued with other anti-seizure medications except lacosamide, which was tapered off. A genetic study was not possible due to monetary constraints. The child’s seizure control and behaviour improved significantly at follow-up. The parents provided written informed consent to report their child’s case.

The diagnosis of SSPE is catastrophic for both the child and the caregivers. An atypical presentation of SSPE often leads to misdiagnosis, especially in the early stages [4]. The disease is rare in developed countries. Currently, India is one of the countries with the highest burdens of the disease. Many Indian SSPE children are lost to follow-up in the wake of being told the prognosis of the disease. With increasing awareness, more children with SSPE with atypical presentations are being seen [5-7]. Despite the high incidence of SSPE in India, an accurate and early diagnosis remains a challenge. In the case presented herein, the combination of cognitive decline, myoclonus, periodic/quasiperiodic high amplitude epileptic discharges, and evidence of intrathecal measles antibody positivity (CSF/serum ratio, 33.8) was highly suggestive of SSPE. However, acute-onset GTCS as the type of seizure marking the beginning of illness and the absence of a history of clinical measles in a vaccinated child were the red flags that mandated a further evaluation of the child. With such a debilitating course, one of the possibilities was fulminant SSPE, which comprises approximately 10% of all cases of SSPE [8]. GTCS, focal tonic seizures, and other seizure types have been mentioned in the literature as atypical presentations of SSPE, which delay the diagnosis of SSPE until classical features appear [8-10]. Three patterns of EEG findings have been mentioned, with periodicity being common to all. In the current case, initial EEG showed quasiperiodic bursts of high-amplitude delta waves lasting for 0.5 to 3 seconds, although there was no evidence of polymorphic waves to suggest the classical “Radermecker complexes.” The initial EEG findings did not point against the diagnosis of SSPE, but subsequent EEG findings clearly did not favour SSPE. A stormy onset of myoclonic seizures with cognitive stagnation or regression is well known in children with MAE. Usually children tend to have their first seizure by 4 years but seizure onset can be as late as 6 years. The initial EEG can be normal, while generalised 2 to 5 Hz spike wave discharges appear later. These children may also have GTCS and absence seizures. This child developed GTCS first, followed by head drop, and absence seizures appeared last with classical EEG findings. Autoimmune encephalitis is the closest mimicker of SSPE, with clinical similarities and CSF measles antibody positivity [11]. This treatable disorder can
masquerade as SSPE, which is progressive and fatal. Hence, this child was given immunotherapy with initial partial response. What remains unexplained in this case is the high CSF measles antibody titres. Damage to the blood-brain barrier due to any cause may lead to a false elevation of intrathecal CSF measles antibody titres. However, to the best of our knowledge, elevated CSF antibodies in MAE have not been reported in the literature. The positive serology in the current case, with decreasing titres from a laboratory and a subsequent negative report from another laboratory, combined with the electroclinical evolution of symptoms helped us to rule out SSPE. The difference in results from different laboratories can be explained either by differences in the dilution standardisation used by different laboratories (1:2 or 1:4 dilution) or a coincidental subclinical measles infection in the child. However, the findings of normal CSF biochemistry suggest that the blood-brain barrier was intact; hence, the second hypothesis is less likely as the finding of elevated CSF antibodies could not have been a simple reflection of an increased serum antibody titre. SSPE has no diagnostic brain MRI findings except posterior predominant white matter signal changes [12].

As this case illustrates, the diagnosis of SSPE in a child with an atypical presentation should ideally be one of exclusion, and the child should be evaluated for treatable underlying causes. SSPE should be diagnosed only after careful consideration of the clinical course. Clinicians should not be biased towards the diagnosis of SSPE by positive serology in the absence of other strong indicators.

A child with MAE who presents in an unusual way may be misdiagnosed with SSPE. Positive measles antibody titres should be strongly supported by clinical and EEG features to confirm the diagnosis of SSPE.

This study was approved by the Institutional Review Board of Command Hospital Chandimandir (approval number: 1234/Paeds/CHWC). The written informed consent was taken from the parents.

Conflicts of interest

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

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Conceptualization: RS. Data curation: RS and NB. Formal analysis: NB. Methodology: SS. Visualization: AP. Writing-review & editing: RS, SS, and AP.

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References

A Case of Progressive Multifocal Leukoencephalopathy in a Child with Hyper-Immunoglobulin M Syndrome: The Impact of Missed Care during the COVID-19 Pandemic

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Progressive multifocal leukoencephalopathy (PML) is a frequently fatal subacute demyelinating disease of cerebral white matter caused by the human polyomavirus 2, commonly known as the John Cunningham virus (JCV) [1]. PML is primarily reported in patients with severe immunosuppression caused by human immunodeficiency virus (HIV) infection, hematologic malignancy, or immunosuppressive therapy, including natalizumab for multiple sclerosis and rituximab for Crohn’s disease [1]. However, PML has also been reported in primary immunodeficiencies (PID), including those with hyper-immunoglobulin M syndrome (HIGM), common variable immunodeficiency, and Wiskott-Aldrich syndrome [2]. In this case study, we describe PML in an immunocompromised child with HIGM during the coronavirus disease 2019 (COVID-19) pandemic.

A 6-year-old boy with a history of HIGM was examined after experiencing 3 weeks of left-side weakness in June 2021. The patient had a history of recurrent otitis media and pneumonia since 12 months of age and pertussis at 30 months of age. The patient was diagnosed with HIGM after the pertussis workup. The patient had no family history of immunodeficiency, and his development was normal. The patient had been treated with monthly intravenous immunoglobulin (IVIG) replacement therapy, which had been discontinued 7 months previously because the patient’s parents thought it would be risky to visit a hospital during the COVID-19 pandemic and underestimated the risk of opportunistic infections. The patient had been showing fatigue and poor concentration for 3 weeks prior to the visit and decreased left hand and arm movement for 10 days prior to the visit. The patient did not show signs of upper respiratory or gastrointestinal infection symptoms. The patient was mentally alert; however, a physical examination revealed additional central left facial palsy, urinary incontinence, mutism, and cognitive decline. The patient’s motor grade of the left upper extremity was rated as grade III, and the left lower extremity was rated as grade IV. Right upper and lower motor function was intact. No pathologic reflexes were found. Serum inflammatory markers, including C-reactive protein and the erythrocyte sedimentation rate, were within the normal range. Lymphocyte subset counts were also within the normal range for the patient’s age (Table 1). Serum immunoglobulin (Ig) G and IgA levels were extremely low, with
elevated IgM levels (Table 1). Serum HIV antigen and anti-HIV antibodies were not detected. Antibodies against serum anti-myelin oligodendrocyte glycoprotein were absent. The cerebrospinal fluid (CSF) analysis was unremarkable (Table 1). CSF herpes simplex virus polymerase chain reaction (PCR), enterovirus PCR, and oligoclonal band were negative, and no bacteria were grown on the CSF aerobic culture. No acid-fast bacilli or fungi were grown on the CSF culture, and no encapsulated yeast was observed on direct fungal microscopy. Brain magnetic resonance imaging (MRI) with contrast enhancement demonstrated bilateral asymmetric multifocal regions at the subcortical white matter with high signals on the T2-weighted images (Fig. 1). IVIG replacement therapy was initiated due to the low levels of IgG. Although PML was suspected based on the MRI findings and the history of the patient’s immunodeficiency, intravenous methylprednisolone pulse therapy was initiated before other encephalopathies including acute disseminated encephalomyelitis were excluded. JCV PCR tests of the CSF and urine were positive, and the patient was diagnosed with PML. The patient showed partial improvement of facial palsy and lower extremity weakness with slight or no improvement of hand strength and was discharged after 8 days in the hospital. Three weeks after the patient was first admitted, he was readmitted due to worsening of his left-side weakness and an inability to ambulate. The patient’s right hand and leg presented involuntary movements, and the patient could not speak and showed little voluntary movement, such as nodding. Follow-up MRI with contrast enhancement demonstrated worsening of the PML lesions (Fig. 1). Despite 10 additional hospital admissions with periodic IVIG replacement therapy, the disease worsened. Currently, 11 months after the original onset of the disease, the patient is bedridden with a tracheostomy, home ventilation care, and percutaneous intestinal gastrostomy.

X-linked HIGM, which is the most common type of HIGM, is caused by pathogenic variations in the CD40LG gene. A genetic analysis revealed a 4,858-base pair deletion including exon 5 on the CD40LG gene, which encodes CD40 ligand, in this patient. Patients with HIGM syndrome have extremely low levels of serum IgG due to a class-switching recombination defect. Therefore, regular IVIG replacement therapy is important even if it cannot fully prevent opportunistic infections. Unfortunately, this patient did not receive IVIG replacement during the COVID-19 pandemic. In addition, the CD4+ lymphocyte count is not the appropriate indicator of cellular immunity in HIGM patients because T cell counts are not affected by defects in CD40 ligand expression; instead, CD40 ligand mediates T cell interactions with monocytes, macrophages, and dendritic cells [3]. Therefore, an early classification of the type of HIGM via genetic testing or a functional assessment using flow cytometry is important to decide the appropriate prophylactic or corrective treatment.

Hematopoietic stem cell transplantation is the mainstay corrective therapy for HIGM patients with CD40 ligand dysfunction [3]. However, transplant-related complications are also life-threatening, so careful consideration should be given to whom and when stem cell transplantation is performed [4].

The incidence of PML was estimated to be 44 cases per 10,000,000 individuals from 2002 to 2004 in the United States [5].

Table 1. Findings of the serum and cerebrospinal fluid evaluations

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood analysis</strong></td>
<td></td>
</tr>
<tr>
<td>Leukocytes (×10^9/L)</td>
<td>9,500 (0–3)</td>
</tr>
<tr>
<td>Absolute neutrophil count (×10^9/L)</td>
<td>5,260 (1–20)</td>
</tr>
<tr>
<td>Absolute lymphocyte count (×10^9/L)</td>
<td>2,888 (1,200–4,700)</td>
</tr>
<tr>
<td>CD+4 lymphocyte count (×10^9/L)</td>
<td>1,123 (400–2,500)</td>
</tr>
<tr>
<td>CD+8 lymphocyte count (×10^9/L)</td>
<td>531 (200–1,700)</td>
</tr>
<tr>
<td>IgG (mg/dL)</td>
<td>10.6 (608–1,572)</td>
</tr>
<tr>
<td>IgA (mg/dL)</td>
<td>7.5 (33–236)</td>
</tr>
<tr>
<td>IgM (mg/dL)</td>
<td>489.2 (43–207)</td>
</tr>
<tr>
<td><strong>CSF studies</strong></td>
<td></td>
</tr>
<tr>
<td>Leukocytes (×10^9/L)</td>
<td>1 (0–5)</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>76 (40–80)</td>
</tr>
<tr>
<td>Protein (mg/dL)</td>
<td>28.98 (20–40)</td>
</tr>
<tr>
<td>IgG index</td>
<td>73 (0.7)</td>
</tr>
</tbody>
</table>

Values are presented as median (range). CD, cluster of differentiation; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; CSF, cerebrospinal fluid.
Zerbe et al. [2] found 26 reported cases of PML with PIDs. Four of those cases were diagnosed with HIGM. After the publication of Zerbe et al. [2], two additional PML cases with HIGM were reported [6]. This case is the first description of PML associated with HIGM in Korea, to the best of our knowledge. As any area of the brain can be involved, the clinical presentations of PML vary. Common clinical presentations include insidious cognitive dysfunction, aphasia, motor or sensory dysfunction, and coordination and gait difficulties [1,7,8]. Brain MRI of PML typically shows multiple hyperintense lesions on T2-weighted images and the fluid-attenuated inversion recovery sequence in the affected white matter with or without gadolinium enhancement. PML is commonly seen as multifocal lesions in the subcortical white matter of the frontal and parieto-occipital lobes. However, PML involvement is possible anywhere in the brain, and it can be seen as an isolated lesion [8]. The histopathologic features of brain biopsies with PML show a triad of multifocal demyelination, enlarged bizarre astrocytes, and enlarged oligodendrocyte nuclei. A definitive diagnosis of PML requires typical histological findings with evidence of JCV infection in the central nervous system. However, brain MRI features and a clinical presentation consistent with PML with positive JCV PCR in the CSF are also sufficient to diagnose PML, as in this patient [8].

The main goal of PML treatment is immune reconstitution. The introduction of antiretroviral therapy significantly improved the outcomes of HIV-related PML patients. In immunomodulatory drug-induced PML, the discontinuation of these drugs can be considered to improve the patient’s outcome [7]. Therefore, a poor prognosis is anticipated when immune reconstitution is not feasible [7]. In the past few decades, several antiviral therapies, including cidofovir for treating JCV, have been investigated with poor results [1]. There was no decrease in mortality or improvements in disability with cidofovir treatment for HIV-related PML [9]. Cytarabine seemed promising due to its ability to inhibit JCV replication in vitro. Nevertheless, several clinical trials could not show decreased mortality in PML patients treated with cytarabine [1]. JCV-specific therapy to improve cellular immunity, including anti-programmed death-1 (anti-PD-1) antibodies (nivolumab and pembrolizumab) and interleukins, have also been tested over the past few years [7]. However, evaluations are limited to case reports or case series. Further studies are needed to evaluate the exact contributions of these therapies to PML treatment. In this case report, IVIG replacement therapy was inadequate for reconstitution of cellular immunity in this patient, which may indicate a poor prognosis. Therefore, hematopoietic stem cell transplantation should be considered in patients diagnosed with PID with CD40 ligand deficiency [4]. Although immune reconstitution is the mainstay of treatment of PML, it paradoxically can induce PML-immune reconstitution inflammatory syndrome (IRIS), which presents as acute clinical worsening due to the hyperinflammation at the site of the original PML lesions [10]. Contrast enhancement and edema of previous PML lesions in MRI are characteristic of this inflammation, which is not a usual sign in classic PML lesions [1]. It has been shown that steroid therapy can be helpful in PML-IRIS patients [10]. We tried steroid treatment, considering the possibility that this patient may have had another steroid-responsive disease, such as acute disseminated encephalomyelitis, not PML. Another reason for using steroids was to prevent inflammation caused by acute immune reconstitution resulting from IVIG.

Herein, we report a case of PML in a boy with HIGM who discontinued treatment during the COVID-19 pandemic. Although cases of PML are relatively rare in PID and largely reported in adult patients with acquired immunodeficiency, PML should be suspected when a patient with PID shows subacute neurologic symptoms with multifocal brain lesions primarily in the white matter. The present study was approved by the Institutional Review Board of Hallym University Health System (IRB No. 2022-05-017). The board waived the requirement of informed consent.

Conflicts of interest

There is no financial conflict with GENOME INSIGHT Inc.

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References

Microcephaly is defined as a head circumference more than 3 standard deviations (SD) smaller than the typical value in babies of the same sex and age and can result in asymptomatic to severe developmental delays and refractory seizures. Unlike primary microcephaly, which is present at birth, secondary microcephaly is characterized by a normal head circumference when the infant is born and a rapid decrease in head growth thereafter. Secondary microcephaly is also referred to as postnatal microcephaly and is sometimes associated with rare genetic disorders [1]. Intellectual developmental disorder with microcephaly and pontine and cerebellar hypoplasia (MICPCH) is an X-linked disorder affecting females that is characterized by severely impaired intellectual development, microcephaly, and varying degrees of pontocerebellar hypoplasia [2]. Calcium/calmmodulin-dependent serine protein kinase (CASK)-associated MICPCH is extremely rare, and more than 50 females and a few males with MICPCH have been described in the medical literature [3]. Here, we report a very rare Korean case of an infant with MICPCH with a CASK mutation. This case was reviewed and approved by the Institutional Review Board of Keimyung University Dongsan Hospital (IRB No. 2022-07-032). The requirement for informed consent was waived by the board.

A female infant was born at 40 weeks of gestation by vaginal delivery at a local hospital. There were no remarkable complications during the pregnancy. The infant had a birth weight of 3,200 g (50th percentile), a height of 49.5 cm (50th to 75th percentile), and a head circumference of 33.5 cm (25th to 50th percentile). Immediately after birth, the auditory brainstem response test results were 35 dB on the left and 60 dB on the right and she had hearing aid treatment. She was found to have severe microcephaly (< 1st percentile) persistently in routine infant check-ups (at 2 months), so she underwent brain computed tomography (CT) when she was 5 months old at another clinic. Cerebellar hypoplasia was found on the brain CT. When she came to our clinic (at 6 months), her weight was 7,830 g (50th to 75th percentile), her length was 65.3 cm (25th to 50th percentile), and her head circumference was 37.7 cm (–4 SD [38.1 cm]). She had facial particularities, including an oval face, micrognathia, arched eyebrows, hypertelorism, long eyelashes, epicanthus, low-set and prominent ears, long philtrum,
and a short nose with a broad nasal bridge and tip (Fig. 1). A small anterior fontanelle was found in the physical examination. The physical examination also found increased muscle tone in the lower extremities. Brain magnetic resonance imaging (MRI) findings showed microcephaly with diffuse smooth gyral markings of the cerebral cortex, and pontocerebellar hypoplasia (Fig. 2). Congenital viral and metabolic workup test results were all normal. Her family history was not significant, and her parents were healthy and denied consanguinity.

Conventional chromosomal analysis revealed a normal female karyotype (46, XX). In next-generation sequencing (hereditary microcephaly panel), the heterozygote c.2400C > G (p.Tyr800Ter) variant was found in the CASK gene. The CASK gene is the causative gene of intellectual developmental disorder and MICPCH (OMIM #300749), which is inherited in an X-linked dominant manner and is characterized by severely impaired intellectual development and varying degrees of pontocerebellar hypoplasia. The patient’s features and symptoms were consistent with those of MICPCH. CASK c.2400C > G is a novel variant that has not been reported in previous publications or in normal population databases, including gnomAD/ExAC (https://gnomad.broadinstitute.org/), the 1000 Genomes Project (http://1000genomes.org), and the Korean Reference Genome Database (http://coda.nih.go.kr/coda/KRGDB/) (PM2). Loss-of-function is a well-known mechanism of disease associated with the CASK gene, and c.2400C > G (p.Tyr800Ter) is a null variant expected to cause nonsense-mediated decay (PVS1). Whether this variant occurred de novo or was inherited in this case could not be determined because the parents refused genetic testing. However, neither parent showed any specific symptoms or abnormal findings, and the penetrance of MICPCH is known to be complete, so the probability of a de novo variant is very high. According to the 2015 American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines, we applied PVS1 and PM1 as evidence of pathogenicity and interpreted this to be a likely pathogenic variant. The patient had no seizures and showed developmental delays at 6 months. All developmental domains were at the level of 3 to 4 months. She is undergoing continuous rehabilitation treatment and follow-up.

CASK-related disorders have two main clinical phenotypes, including (1) MICPCH, which primarily affects females and generally is associated with pathologic loss-of-function variants in the CASK gene and (2) X-linked intellectual disability with or without...
nystagmus has been reported in males and females, and is generally associated with hypomorphic CASK pathogenic variants such as missense variants and in-frame deletions [4]. Mental retardation and MICPCH are diagnosed in females with severe intellectual disabilities and progressive microcephaly, and usually include epileptic seizures [4]. The head circumferences initially range from normal to mild microcephaly (approximately –2 SD), followed by mild to severe progressive postnatal microcephaly (less than –10 SD) around 4 months of age [5]. Patients have characteristic facial malformations (broad forehead, oval face, arched eyebrows, hypertelorism, epicanthus, macrotia, long philtrum, short nose with a broad bridge, large eyes, and micrognathia) and ophthalmic (nystagmus, optic nerve hypoplasia, glaucoma, and myopia) and auditory (hearing loss in about 25% of cases) manifestations [2,5]. Neurological symptoms such as seizures (about 40% of the patients), hypotonia, extremity hypertonia, or dystonia may also occur [4]. Only about 25% of the patients can walk, and most of them do not develop language for communication [3,6]. The patient in our case also showed severe microcephaly after birth, and a broad forehead, small chin, arched eyebrows, long eyelashes, large ears, long philtrum, broad nose bridge, and short nose with tip were observed, which are findings consistent with MICPCH. In this case, too, there was hearing loss immediately after birth, which is thought to be a symptom of MICPCH. To date, more than 70 CASK mutations have been identified and reported, and CASK mutations have been shown to manifest as a wide range of phenotypes [7]. However, the disease has several common features, including severe developmental delay, severe postnatal microcephaly under 1 year of age, and with or without extremity hypertonia and postnatal growth retardation [7].

The CASK gene is located at Xp11.4 and is a member of the membrane-associated guanylate kinase protein family. CASK is believed to manipulate the formation and activity of synapses by controlling presynaptic tissue and neurotransmitter release. In addition, CASK can modulate gene expression involved in cortical development, maintain dendrite morphology, and control ion channels to their post-synaptic locations [8]. Due to the location of CASK on the X chromosome, MICPCH usually results from loss-of-function mutations and is overrepresented in females due to early male mortality [9].

The MRI findings of mid-hind brain hypoplasia and normal or large corpus callosum in girls with microcephaly and neurodevelopmental retardation may suggest a possible CASK mutation [2,10]. In brain MRI examinations of patients with CASK mutations, the supratentorial abnormalities included delayed myelination and progressive cortical atrophy, simple gyrus, subcortical high T2 signal abnormality in the frontal cortex, and venous hemangioma [2-4]. The MRI findings in our case showed the same results as in other studies, and normal corpus callosum and diffuse smooth gyral markings of the cerebral cortex were also observed.

To date, fewer than 100 cases of MICPCH have been reported, making it a very rare disease. Our patient presented a previously unreported mutation in the CASK gene consistent with the MICPCH phenotype. We believe that the description of this case may be useful in expanding our knowledge of MICPCH syndrome.

**Conflicts of interest**

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

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**References**


Corrigendum: Clinical Characteristics and Neurologic Outcomes of X-Linked Myotubular Myopathy

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Before correction
The Institutional Review Board (IRB) of the Seoul National University Hospital approved this study (IRB no. 1101-110-353) and waived the requirement for informed consent.

After correction
The Institutional Review Board (IRB) of the Seoul National University Hospital approved this study (IRB no. 2204-177-1320) and waived the requirement for informed consent.

The authors apologize for any inconvenience that it may have caused.
Instructions to authors

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

8) The number of pages of manuscripts of reviews and original articles has no limitation but no more than 10 printed pages are recommended. Letters to editor should be written in a maximum of 3 printed pages.

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

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

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

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

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

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

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

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

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

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

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Examples of reference styles

1) Journal article

2) Book
- Book
- Book chapter
- Abstract book or conference proceedings
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1) Each table should be inserted on a separate page, with the table number, table title and legend.
2) The numbers of tables should be in Arabic numerals in their order of citation.
3) Titles of tables should be concise using a phrase or a clause. The first character should be capitalized.
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6) Unnecessary longitudinal lines should not be drawn. Horizontal lines should be used as sparingly as possible.
7) All symbols and abbreviations should be described below the table.
8) Use superscript letters (a, b, c) to mark each footnote and be sure each footnote in the table has a corresponding note. List abbreviations in the footnote section and explain any empty cells.
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1) Figures should be submitted separately from the text the manuscript. All pictures and photographs should be of excellent quality and supplied as JPEG or TIFF files with resolution of more than 300 dpi. The preferred size of figure is 7.4×10.0 cm (3×4 inches). Except for particularly complicated drawings that show large amounts of data, all figures are published at one page or one column width. All kinds of figures may be reduced, enlarged, or trimmed for publication by the editor.
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which the figures are referred to in the main text. In cases where more than two photographs are used with the same number, alphabet characters should be used next to the Arabic numeral (e.g.: Fig. 1A, Fig. 1B).

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Brief communications should include a concise and timely original research, a preliminary study, and significant material for rapid dissemination. It should contain a structured abstract (no more than 150 words), main text (less than 2,000 words), no more than 3 illustrations (figure or table), and no more than 20 references. The main text should be written under the heading “Findings”. Subheadings should not be used but the text should chronologically consist of a short background, aim, materials and methods, a short and focused discussion and a brief conclusion (but without including subheadings). Supplementary materials can be published online.

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

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Letters to the editor should be a brief description with short discussions on any topics that attract attention of journal readers. It should be brief, clear and conclusive. And it should be accompanied by a statement that written consent to publish was obtained from the patient(s). No abstraction is required. Body of the letter has no structure and the word count is limited to 1,500 words. It should be written in a maximum of 3 printed pages, less than 10 references, less than 2 tables or figures, and less than 5 authors.

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

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1. General provisions
   □ The authors should ensure that the contents of the present manuscript have not been published nor intended to be published in other journals.
   □ The manuscript should be formatted as follows: A4 paper, 12 point font, left-aligned, double-spaced.
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   □ The abstract should be divided into Background and Purpose, Methods, Results, and Conclusions; it should be written in one paragraph that is within 250 words.
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   □ In-text citations should be numbered and should correspond to the numbers in the references.
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적절한 습관과 관리에 의해 중재되어야 한다. 항뇌전증약을 복용한 환자에서 자살충동 또는 자살행동을 보이는 위험성

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석의 치료(4세 이상) - 소아 간대성 근경련 뇌전증(Juvenile Myoclonic Epilepsy) 환자의 근간대성 발작의 치료(4세 이상) 2. 부가요법 - 기존 1차 뇌전증치료제 투여로 적절하게 조절이 되지 않는 2차성 전신발작을 동반하거

신기능이 약화된 노인 환자에서 용량조정이 권장된다.

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적절한 습관과 관리에 의해 중재되어야 한다. 항뇌전증약을 복용한 환자에서 자살충동 또는 자살행동을 보이는 위험성

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경증

고 있는 환자, 또는 관련 심장 질환 또는 전해질 장애가 있는 환자에게 투여 시 주의하여야 한다.

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에 대하여 모니터링되어야 한다. 항뇌전증약을 처방받는 뇌전증과 다른 많은 질병은 그 자체가 이환 및 사망, 치료기간 동안

적절한 습관과 관리에 의해 중재되어야 한다. 항뇌전증약을 복용한 환자에서 자살충동 또는 자살행동을 보이는 위험성

의 치료(12세 이상) - 특발성 전신성 뇌전증(Idiopathic Generalized Epilepsy) 환자의 1차성 전신 강직-간대 발작의 치료(12세 이

신경정신과적 이상반응

석의 치료(4세 이상) - 소아 간대성 근경련 뇌전증(Juvenile Myoclonic Epilepsy) 환자의 근간대성 발작의 치료(4세 이상) 2. 부가요법 - 기존 1차 뇌전증치료제 투여로 적절하게 조절이 되지 않는 2차성 전신발작을 동반하거

신기능이 약화된 노인 환자에서 용량조정이 권장된다.
트리렙탈®은 NICE GUIDELINE에서 성인 및 소아 부분 발작 환자의 일차 단독요법 또는 보조요법으로 권고되고 있습니다.¹

Reference

Product Information
※ 상세 제품 정보는 QR 코드 또는 식품의약품안전처 의약품통합정보시스템 (https://nedrug.mfds.go.kr)을 통해 확인하여 주시기 바랍니다.

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\(^{1}\) AED : antiepileptic drug, ESL : eslicarbazepine acetate