Aims and scope

*Annals of Child Neurology* is an interdisciplinary peer-reviewed biomedical journal publishing articles in the fields of child neurology, pediatric neurosurgery, pediatric neuroradiology, child psychiatry, pediatric neuropsychology, developmental and behavior pediatrics, pediatric neuroscience, and developmental neurobiology. The aims of *Annals of Child Neurology* are to contribute to the advancements in the fields of pediatric neurology through the scientific reviews and interchange of all of pediatric neurology. It aims to reflect the latest clinical, translational, and basic research trends from worldwide valuable achievements. In addition, genome research, epidemiology, public education and clinical practice guidelines in each country are welcomed for publication.

Focusing on the needs of neurologic patients from birth to age 18 years, *Annals of Child Neurology* covers topics ranging from assessment of new and changing therapies and procedures; diagnosis, evaluation, and management of neurologic, neuropsychiatric, and neurodevelopmental disorders; and pathophysiology of central nervous system diseases.

Area of specific interest include the following:
behavioral neurology & neuropsychiatry, clinical neurophysiology, epilepsy, headache medicine, neurocritical care, neurodevelopmental disabilities, neurogenetics, neuromaging, neuromuscular medicine, 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, reviews, letters to the editor. The editorial board invites articles from international studies or clinical, translational, and basic research groups. Supplements can be published when they are required.

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On behalf of the Editorial Board of *Annals of Child Neurology* and my co-editors, it is my great pleasure to announce the official publication of 1st Issue of *Annals of Child Neurology*. 2019 is a pivotal year of this journal to mark a new path. After full discussion with the key committees of the Korean Child Neurology Society, we have decided to make a tremendous change in the scope of the journal. It is our intention to transform the *Journal of the Korean Child Neurology Society* into an international, open access journal called *Annals of Child Neurology*, which is to publish up-to-date, high-quality, basic and clinical research papers, relevant review articles, alongside letters to editors. The journal covers a variety of different topics ranging from epidemiology, etiologies, pathophysiology, brand-new or changing diagnostic procedures and management of neurologic, neuropsychiatric, neurodevelopmental conditions to all other related conditions. Any closely connected or relevant papers will be appreciated and will make a substantial contribution to the success of this journal.

We have drastically expanded the numbers, geographical distribution, breadth of editorial board members to compensate for potential short comings and further enrich this journal. It is my sincere hope that the journal will inspire innovative, interdisciplinary possibilities, make new ways to ‘never-thought-before’ concepts. As always, we welcome and encourage constructive feedback and commentaries. If you have any questions or concerns, please feel free to contact at editor@annchildneurol.org.

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

**Conflicts of interest**

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

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In this article, we reviewed current knowledge regarding gene-specific therapies for some developmental and epileptic encephalopathy caused by genes with high diagnostic yields, and which are therefore, also more frequently encountered by physicians during treatment, including ALDH7A1, CDKL5, KCNQ2, KCNT1, SCN2A, SCN8A, STXBP1, and SYNGAP1. Among these therapies, the ones directly targeting causative mutations are retigabine in KCNQ2 encephalopathy and quinidine in KCNT1 encephalopathy. However, despite promising results in vitro, the outcomes related to these therapies were disappointing when administered to patients. Considering the pathologic mechanisms of causative mutations, sodium channel blockers are recommended for patients with KCNQ2 mutations, infantile epileptic encephalopathy patients with SCN2A mutations, and patients with SCN8A mutations. Levetiracetam can be considered for patients with STXBP1 mutations.

Keywords: Epilepsy; Precision medicine

Introduction

With the advent of next-generation sequencing, there have been significant advances in the genetics of epilepsy within the last decade [1]. In developmental and epileptic encephalopathy patients, targeted gene panels and/or whole exome sequencing have now become part of the routine diagnostic workup, which provide a genetic diagnosis in about 30% of patients.

As the number of genetically diagnosed patients has increased, so has the demand for more precise treatment based on pathogenic genetic mutations. The demand has resulted in active research and a rapidly increasing number of publications focused on precision medicine in epilepsy (Fig. 1) [2]. Based on current knowledge, approximately 25% of genetically diagnosed epilepsy patients with de novo monogenic mutations carry potential targets for precision medicine approaches [3].

In this article, we review current knowledge regarding gene-specific therapies for some forms of developmental and epileptic encephalopathy caused by genes with high diagnostic yields, which are therefore, more frequently encountered by treating physicians.

ALDH7A1

The aldehyde dehydrogenase 7 family, member A1 (ALDH7A1) gene encodes the enzyme α-aminoadipic semialdehyde (α-AASA) dehydrogenase, also known as antiquitin, a key enzyme in lysine metabolism [4]. Biallelic mutations of ALDH7A1 result in deficiency of α-AASA dehydrogenase, which then results in the accumulation of α-AASA and the cyclic equivalent Δ1-piperideine-6 carboxylate (Δ1-P6C) [4]. The accumulated Δ1-P6C sequesters
the active form of vitamin B6 (pyridoxal 5′-phosphate [PLP]), and causes pyridoxine-dependent epilepsy [4].

The classic presentation of pyridoxine-dependent epilepsy is the neonatal onset of treatment-resistant seizures that respond dramatically, both clinically and electroencephalographically, to pyridoxine supplementation [5]. Despite adequate seizure control achieved with pyridoxine alone, 75% of patients with pyridoxine-dependent epilepsy have significant intellectual disability and/or developmental delay [6]. The degree of intellectual disability or developmental delay does not correlate with seizure control or the age at which pyridoxine treatment is initiated [6].

Treatment with pyridoxine supplementation in pyridoxine-dependent epilepsy patients is therapeutic because it overcomes the secondary depletion of pyridoxal phosphate (PLP) [5]. Pyridoxine supplementation alone does not treat the underlying defect of lysine oxidation, but treatment with a lysine-restricted diet and/or with a lysine transport inhibitor (arginine) has been shown to improve cognitive function at some level [7–9]. Triple therapy with pyridoxine, arginine supplementation, and dietary lysine restriction has been recommended to ameliorate the cognitive impairment seen in pyridoxine-dependent epilepsy [9].

**CDKL5**

Cyclin-dependent kinase-like 5 (CDKL5) encephalopathy is a severe X-linked neurodevelopmental disease caused by mutations in the *CDKL5* gene, which lead to deficiency in CDKL5 protein expression or function [10]. CDKL5 is highly expressed in the brain, mainly in neurons, with both nuclear and dendritic localization, and its expression peaks during the postnatal period [11,12]. In mouse models, Cdlk5 knockout animals exhibited hippocampus-dependent learning and memory impairment, visual and respiratory deficits, and motor stereotypes, which were associated with neuroanatomical alterations such as reduced dendritic branching of hippocampal and cortical neurons, reduced dendritic spine density, and altered connectivity [13–19].

Epilepsy in CDKL5 encephalopathy patients often starts before 2 months of age, with frequent generalized tonic seizures that typically last for less than 1 minute [20]. Seizures at this time are well-controlled with antiepileptic drugs (AEDs), and electroencephalograms (EEGs) are usually normal [20]. Epilepsy relapses in late infancy at a median age of 11 months, when infantile spasms with hysparrhythmia, sometimes combined with brief tonic medication-resistant seizures, emerge [20]. During the year after onset of infantile spasms, epilepsy evolves into late multifocal and myoclonic epilepsy, showing frequent pharmacoresistant seizures of multiple types such as myoclonic seizures, and EEGs showing high-amplitude delta waves with pseudo-periodic bursts of high-amplitude spikes [20]. Severe neurodevelopmental delay is present from the beginning, but there is usually no period of regression [21].

Seizures in CDKL5 encephalopathy, especially seizures during the “late epilepsy” stage are highly refractory, and there are no available AEDs that are effective in controlling these seizures. A promising study regarding cannabidiol came out in 2018, which analyzed patients with treatment-resistant, childhood-onset epilepsies including CDKL5 encephalopathy [22].
patients (n = 17), 50% responder rate was 41% at week 12, and 53% by week 48 [22]. However, cautious interpretation is needed due to the small number of subjects and due to exclusion of withdrawn patients from analysis. Therefore, additional placebo-controlled randomized trials with larger sample sizes are needed.

Several labs are assessing the use of drugs such as tianeptine and tideglusib in CDKL5 encephalopathy. Tianeptine is an antidepressant that has been used for more than 30 years. Studies utilizing neurons from Cdkl5 knockout mouse models have proposed that CDKL5 deficiency in primary hippocampal neurons negatively affects the expression of the alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, and such an effect is likely to contribute, at least in part, to the altered synaptic functions and cognitive impairment linked to loss of CDKL5 [23]. Therefore, tianeptine, which is known to recruit and stabilize AMPA receptors at the synaptic sites, has been studied in vitro and results revealed that tianeptine normalized the expression of membrane-inserted AMPA receptors [23].

Tideglusib is a glycogen synthase kinase 3 beta (GSK3β) inhibitor, and is currently undergoing clinical trials for use against diseases such as Alzheimer’s, progressive supranuclear palsy, and myotonic dystrophy. In mouse, deficiency of Cdkl5 caused defects in postnatal hippocampal development and hippocampus-dependent learning and memory. These defects were accompanied by increased activity of GSK3β, an important inhibitory regulator of many neuronal functions [17]. Therefore, tideglusib was tested on Cdkl5 knockout mice and results showed that tideglusib improved hippocampal development, hippocampus-dependent behaviors, and memory performance in juvenile Cdkl5 knockout mice [24].

Finally, CDKL5 protein substitution therapy was successfully conducted in a mouse model using a protein transduction domain (TAT) that was able to deliver macromolecules into cells, and even into the brain when fused to a specific protein [25]. Intracerebroventricular infusion of TAT-CDKL5 protein was efficiently internalized by target cells, which resulted in the retention of CDKL5 activity and the restoration of hippocampal development, hippocampus-dependent memory, and breathing pattern in Cdkl5-null mice [25]. Systemically administered TAT-CDKL5 protein also crossed the blood-brain barrier, reached the central nervous system, and improved behavioral defects in mice [25].

### KCNQ2

Mutations in the potassium channel, voltage-gated, KQT-like subfamily member 2 (KCNQ2) gene, encoding voltage-gated K+ channel subunits underlying the neuronal M-current, usually lead to loss-of-function of K_v7.2 and cause a decrease in neuronal M-current conductance, thereby increasing neuronal excitability [26]. Functional studies have revealed that a 25% reduction in K_v7.2 current is sufficient to increase neuronal excitability to epileptogenic levels in early infancy [27]. However in rare cases, variants of KCNQ2 such as R144Q, R198Q, R201C, and R201H, produce gain-of-function effects and are reported to be associated with early-onset epileptic encephalopathy, infantile spasms, or neonatal nonepileptic myoclonus [28-30].

Benign familial seizures of early infancy and early infantile epileptic encephalopathy (EIEE) are two main types of epilepsy associated with KCNQ2 mutations. Seizure onset in both syndromes occurs as early as in the first days of life [31]. Patients with benign seizures in early infancy have an excellent prognosis regarding both seizure remission and neurodevelopment. In contrast, patients with EIEE suffer from a severe phenotype comprising drug-resistant seizures, intellectual disability, and encephalopathic EEG [31].

A systematic review conducted in 2019 analyzed the medications used in EIEE, and revealed that sodium channel blockers were the most frequently used monotherapy agent [31]. The distribution of AEDs used by patients achieving control of their seizures was 37.8% with sodium channel blockers, 26.3% with valproic acid, and 33.3% with levetiracetam [31]. Treatment trials with phenobarbital were largely unsuccessful: 8.6% of the trials led to seizure freedom in patients while 74.3% of the trials showed no effect [31]. Therapeutic response to sodium-channel blockers in patients with KCNQ2 mutations could be explained by the fact that voltage-gated sodium channels and KCNQ potassium channels co-localize at critical locations on the neuronal membrane and therefore, modulation of one channel may significantly affect the function of the channel complex [32,33]. Because of this, sodium channel blockers such as phenytoin, carbamazepine, and oxcarbazepine are recommended as a first-line treatment [31,34]. However, sodium channel blockers were not clearly superior to levetiracetam or valproate, indicating that the latter AEDs might be considered in patients who failed to respond to sodium channel blockers [31].

Retigabine (also known as ezogabine) is a K_v7.2/K_v7.3 opener that leads to neuronal hyperpolarization of the membrane potential and was first introduced as an adjunctive therapy in adults with focal seizures [35]. Despite its effectiveness, retigabine was withdrawn from the market due to lack of demand caused mainly by side effects such as blue discoloration of skin and retina [36]. However, the fact that retigabine opens the K_v7 potassium channel drew interest in its use for patients with KCNQ2 mutations, and the results were favorable in animal models [37]. Of all mono-therapeutic treatment trials with retigabine, only 14.3% led to
seizure freedom while 71.4% showed no effect and current findings do not support use of retigabine compared to other drugs such as sodium channel blockers [31].

**KCNT1**

The potassium channel subfamily T member 1 (KCNT1) gene encodes the sodium-activated potassium channel KCa4.1. KCNT1 is widely expressed throughout the brain, as well as in the dorsal root ganglia, kidney, and heart, and is responsible for slow hyperpolarization after bursts of action potentials [38,39]. The pathogenic KCNT1 mutations described to date are all missense variants; no nonsense or other truncating mutations have been identified yet [40]. This suggests that perturbation of normal KCNT1 protein function, rather than the loss of its function, is the underlying pathomechanism [40]. This is consistent with other reports, including animal models demonstrating that KCNT1 pathogenic variants manifest a gain-of-function effect with increased current amplitude [39,41,42].

Mutations in KCNT1 cause a wide spectrum of epileptic disorders with variable ages at onset and cognitive outcomes including Ohtahara syndrome, West syndrome, and severe nocturnal frontal lobe epilepsy (NFLE). However, epilepsy of infancy with migrating focal seizures (EIMFS) and autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) are the two most characteristic epilepsies associated with KCNT1 [39,41,43,44]. KCNT1 is the most frequently identified genetic cause of EIMFS, and 39% (28 out of 71) of individuals from EIMFS patient cohorts that have been analyzed for KCNT1 mutations are mutation positive [40]. Patients with ADNFLE and NFLE with KCNT1 mutations have a more severe phenotype than ADNFLE patients with mutations in nicotinic acetylcholine receptor subunit genes in terms of earlier age of seizure onset, marked increase in frequency of refractory seizures, and high frequency of comorbid intellectual disability and psychiatric features [44].

Quinidine is an inhibitor of several types of potassium channels, including KCNQ1, and is currently used as an antiarrhythmic agent and antimalarial drug [40,45,46]. Given that functional studies have shown mutations in KCNT1 cause an increase in channel current, quinidine gathered interest as a potential inhibitor that could reverse this abnormal channel function and therefore, treat seizures in patients with mutations in KCNT1 [41,42,47,48]. Indeed, the effectiveness of quinidine in reversing the increased current of mutant KCNT1 channels has been demonstrated in vitro [42,48]. However, in an order-randomized, blinded, placebo-controlled, crossover trial of quinidine in six ADNFLE patients, 33.3% (n = 2) of patients discontinued therapy due to prolonged QT interval occurring at serum quinidine levels below the therapeutic range, and none of four patients who completed treatment trial showed 50% seizure reduction [49]. Other reports that included 25 EIMFS, two focal epilepsy, one West syndrome, and one NFLE patients, demonstrated that 31.0% (n = 9, including eight EIMFS) of patients experienced improvements in seizure activity due to quinidine administration while the others did not show any improvements [39,48,50-60]. Lack of therapeutic response observed in the majority of patients is likely because exposure levels in the brain are too low to cause significant in vivo channel blockade [52].

**SCN2A**

The sodium channel, voltage-gated, type II, alpha subunit (SCN2A) gene encodes the neuronal sodium channel Na\(_{\text{V}}\)1.2, one of four sodium channel paralogs expressed throughout the central nervous system, along with Na\(_{\text{V}}\)1.1 (SCN1A), Na\(_{\text{V}}\)1.3 (SCN3A), and Na\(_{\text{V}}\)1.6 (sodium channel, voltage-gated, type VIII alpha subunit [SCN8A]) [61]. Mutations in SCN2A are primarily associated with three distinct disorders: (1) infantile epileptic encephalopathy characterized by drug-resistant seizures with age of onset less than 12 months, followed by neurodevelopmental delay; (2) benign (familial) infantile seizures characterized by seizure onset at less than 12 months of age, which resolve by 2 years of age without overt long-term neuropsychiatric consequences; and (3) autistic spectrum disorder/intellectual disability (ASD/ID) characterized by global developmental delay, particularly of social and language milestones, with up to one-third of children developing childhood-onset seizures after 12 months of age [61-63].

An integrated analysis of genetic and electrophysiological data suggested a model explaining the three disorders associated with SCN2A (Fig. 2) [61]. Variants associated with gain-of-function of Na\(_{\text{V}}\)1.2 channel activity led to infantile epileptic encephalopathy and benign infantile seizures, while those associated with loss-of-function led to ASD/ID [62,63]. Further, the degree to which the gain-of-function variants potentiate Na\(_{\text{V}}\)1.2 activity distinguishes infantile epileptic encephalopathy from benign infantile seizures, with severe variants leading to infantile epileptic encephalopathy [62,63]. This model is supported by several other findings including observations using in vitro electrophysiology, the restriction of protein truncating variants resulting in loss of function in ASD/ID cases, shared symptoms between individuals with recurrent missense variants, and the clustering of infantile epileptic encephalopathy/benign infantile seizure variants around the voltage sensor domain of the channel while the ASD/ID missense variants cluster near the pore loop regions [62,63].
Seizures in SCN2A encephalopathy are often resistant to AEDs. However, for infants less than 4 months of age, sodium channel blockers such as phenytoin and carbamazepine are more effective, which is expected considering the gain-of-function nature of causative mutations [62,63]. For children more than 12 months of age with ASD/ID and childhood-onset seizures, the opposite action should be taken, and drugs other than sodium channel blockers, such as levetiracetam, benzodiazepines, and valproate, are therapeutic options. New emerging therapies such as bromides, fenfluramine, and cannabidiol are being studied and have shown efficacy in treating Dravet syndrome [64]. Whether such medications would provide benefit with SCN2A associated late-onset seizures remains unknown. However, when considering such treatments, it is important to remember that the Na\(_{1.1}\) channels affected in Dravet syndrome are more commonly expressed in inhibitory neurons, and that loss-of-function of Na\(_{1.1}\) may have opposing effects in brain networks compared with Na\(_{1.2}\) loss-of-function in excitatory neurons [65].

**SCN8A**

The SCN8A gene encodes the pore-forming voltage-gated sodium channel subunit Na\(_{1.6}\), which is widely expressed in the brain and is responsible for the initiation and propagation of neuronal action potentials contributing to regulation of neuronal excitability [66-68]. Most mutations identified in SCN8A result in gain-of-function changes in biophysical properties leading to elevated channel activity, either due to premature channel opening or impaired channel inactivation [69-73]. However, a small subset of mutations cause loss of function of SCN8A, resulting in isolated intellectual disability, myoclonus, and movement disorders [74,75].

SCN8A encephalopathy patients usually show severe developmental delay and intellectual disability, pharmacoresistant epilepsy with seizures starting before 18 months of age, in addition to pyramidal and extrapyramidal signs [76,77]. Epilepsy in SCN8A encephalopathy patients comprises multiple seizure types, including focal, generalized, and epileptic spasms [78]. Sudden unexpected death in epilepsy is reported in approximately 10% of cases [77]. As SCN8A epileptic encephalopathy is mostly due to gain-of-function mutations of SCN8A, the most effective AEDs reported so far are sodium channel blockers including phenytoin, carbamazepine, and oxcarbazepine, usually at supratherapeutic doses [77]. Also, at least one study reported improvements in seizure clusters and non-convulsive status epilepticus when patients were treated with benzodiazepines [77]. Of note, levetiracetam was reported to be ineffective and may even worsen seizure activity [77].

**STXBP1**

The syntaxin-binding protein 1 (STXBP1) gene encodes the STXBP1 protein, which is an essential protein for presynaptic vesicle docking and fusion through interaction with the soluble N-ethylmaleimide sensitive factor attachment protein receptor (SNARE) complex proteins, and has an essential function in neurotransmitter release [79,80]. STXBP1 encephalopathy is caused by both truncating and missense mutations in STXBP1, and the current leading hypothesis is that STXBP1 loss-of-function is the common pathomechanism, although some in vitro studies have reported possible dominant-negative effects or gain in pathological function [80-83].

STXBP1 encephalopathy patients show developmental delay/intellectual disability, epilepsy, autism spectrum disorders, and involuntary movements such as spasms and jerks [84,85]. Epilepsy in STXBP1 encephalopathy patients is characterized by early onset of tonic spasms, often immediately after birth, and drug-resistant seizures with multifocal epileptic activity on EEG [86].

Some case reports are currently available, and some beneficial AEDs include vigabatrin, valproic acid, and levetiracetam [81,82,87-91]. A beneficial effect of levetiracetam is noteworthy because it has been proposed to modulate synaptic vesicle release via binding with synaptic vesicle glycoprotein 2a [80,92]. However, there is insufficient data for this generalization. There is currently no drug on the market that directly targets STXBP1.
SYNGAP1

The synaptic RAS-GTPase-activating protein 1 (SYNGAP1) gene encodes SYNGAP1 protein, which is an important mediator in the N-methyl-D-aspartate (NMDA) receptor-activated RAS-signaling cascade that regulates postsynaptic density and formation, development, and maturation of dendritic spines [93,94]. In a mouse model, heterozygous mutations in Syngap1 led to protein truncations and abnormal dendritic spines during development [95], decreasing the ability of Syngap1 to bind downstream molecules in the signaling pathway, and thus failing to inhibit Ras activity. Increased Ras activation led to the activation of molecules that regulate the actin cytoskeleton, thus shifting the equilibrium towards the more stable actin form [93,96].

This, combined with an increase in insertion of AMPA receptors into the postsynaptic membrane during development, caused the dendritic spines to mature into mushroom-shaped spines earlier than normal, leading to elevated excitatory synaptic transmission and excitatory/inhibitory imbalance. The occurrence of these events during a critical period of development made the neurons more prone to seizures [93,97].

SYNGAP1 mutations cause developmental epileptic encephalopathy characterized by generalized epilepsy with eyelid myoclonia with absences and myoclonic-atonic seizures that are often pharmacoresistant [98]. Seizures triggered by eating is also a characteristic feature [98]. SYNGAP1 encephalopathy is associated with a spectrum of mild to severe intellectual disability, with a large proportion of patients with severe ID and other comorbidities.

Table 1. Summary of clinical presentations and recommended therapies by causative genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Clinical presentations</th>
<th>Medications</th>
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<tbody>
<tr>
<td>ALDH7A1</td>
<td>Neonatal onset drug resistant seizures which respond dramatically to pyridoxine; Developmental delay/intellectual disability irrespective of pyridoxine supplementation</td>
<td>Pyridoxine, with arginine supplementation and/or lysine restricted diet [9].</td>
</tr>
<tr>
<td>CDKL5</td>
<td>Early infantile epilepsy (&lt;2 months) with very frequent brief drug responsive generalized tonic seizures, followed by infantile spasms with hypsarrhythmia (around 11 months) that are drug resistant, and then drug resistant late multifocal and myoclonic epilepsy (in childhood)</td>
<td>No available medication reported to show significant beneficial effects.</td>
</tr>
<tr>
<td>KCNQ2</td>
<td>Benign familial seizures of early infancy with seizures as early as within first days of life showing excellent prognosis regarding both seizure remission and neurodevelopment</td>
<td>Sodium channel blockers are recommended as first line treatment [31,34]. Levetiracetam or valproate can be used if patients do not respond to sodium channel blockers [31]. Retigabine is inferior to above medications [31].</td>
</tr>
<tr>
<td>KCN1</td>
<td>EIMFS, ADNFLE</td>
<td>Quinidine was not effective in ADNFLE patients [49]. Quinidine showed limited efficacy in EIMFS patients (responder rate=32%, n=25) [39,48,50-60].</td>
</tr>
<tr>
<td>SCN2A</td>
<td>Infantile epileptic encephalopathy with drug-resistant infantile-onset seizures (&lt;12 months) and developmental delay Benign (familial) infantile seizures with infantile-onset seizures (&lt;12 months) that resolve by 2 years of age without neurodevelopmental sequelae Autistic spectrum disorder/intellectual disability with global developmental delay, which 1/3 of patients develop childhood-onset seizures (&gt;12 months)</td>
<td>Sodium channel blockers are recommended for infantile epileptic encephalopathy and benign (familial) infantile seizure patients [62,63]. Drugs other than sodium channel blockers—levetiracetam, benzodiazepines, and valproate—are recommended for autistic spectrum disorder/intellectual disability patients with childhood-onset seizures [61].</td>
</tr>
<tr>
<td>SCN8A</td>
<td>Drug resistant epilepsy with seizure onset age of &lt;18 months and multiple seizure types including focal seizures, generalized seizures, and epileptic spasms, developmental delay/intellectual disability, and pyramidal and extrapyramidal symptoms</td>
<td>Sodium channel blockers are recommended, but supratherapeutic doses can be needed [77]. Levetiracetam can worsen the seizures [77].</td>
</tr>
<tr>
<td>STXBP1</td>
<td>Epilepsy with early onset tonic spasms (often immediately after birth) that are drug resistant, multifocal epileptic activity on EEG, developmental delay/intellectual disability, and involuntary movements such as spasms and jerks</td>
<td>Levetiracetam, vigabatrin, and valproic acid have been reported to be beneficial in small number of case reports [81,82,87-91].</td>
</tr>
<tr>
<td>SYNGAP1</td>
<td>Generalized epilepsy with eyelid myoclonia with absences and myoclonic-atonic seizures that are drug resistant, seizures triggered by eating, and developmental delay/intellectual disability</td>
<td>Valproate and lamotrigine are most frequently used [98].</td>
</tr>
</tbody>
</table>

ALDH7A1, aldehyde dehydrogenase 7 family, member A1; CDKL5, cyclin-dependent kinase-like 5; KCNQ2, potassium channel, voltage-gated, KQT-like subfamily member 2; EEG, electroencephalogram; KCN1, potassium channel subfamily T member 1; EIMFS, epilepsy of infancy with migrating focal seizures; ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; SCN2A, sodium channel, voltage-gated, type II, alpha subunit; SCN8A, sodium channel, voltage-gated, type VIII alpha subunit; STXBP1, syntaxin-binding protein 1; SYNGAP1, synaptic RAS-GTPase-activating protein 1.
ties such as behavioral problems, autism spectrum disorder, hypotonia, eating problems, and sleeping problems [98].

In a retrospective study with 57 patients, valproate (n = 45) and lamotrigine (n = 22) were the most commonly prescribed AEDs, with long-term treatment with lamotrigine in 77% and valproate in 64% of patients, respectively, suggesting effectiveness [98]. This is a reasonable result considering that generalized seizures occur in SYNGAP1-associated epilepsy patients and because there is currently no targeted therapy specifically for SYNGAP1.

Conclusion

Here, we have reviewed several developmental and epileptic encephalopathies caused by frequently identified genes. Already too well known SCN1A was not addressed. Dietary therapy and modulatory therapy such as vagus nerve stimulation were also not covered in this review. Therapies directly targeting at causative mutations, such as retigabine in KCNQ2 encephalopathy and quinidine in KCNT1 encephalopathy were discussed. However, despite promising results in vitro, the results were disappointing when administered to patients. Considering the pathogenic mechanisms of causative mutations, sodium channel blockers are recommended for patients with KCNQ2 mutations, infantile epileptic encephalopathy patients with SCN2A mutations, and patients with SCN8A mutations. Levetiracetam can be considered in patients with STXBP1 mutations. (Table 1).

With a rapidly increasing number of genetically diagnosed patients, development of gene-specific therapies is in great demand. Studies to identify personalized therapeutic strategies based on functional studies of individuals will increasingly be required to meet this demand.

Conflicts of interest

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

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References


Predicting the Outcome of Critically Ill Children and Adolescents with Electroencephalography

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Purpose: Electroencephalography (EEG) is an effective test in predicting severe cortical dysfunction associated with poor outcomes in adult patients, but its value in pediatric patients remains incomplete. Here, we assessed the prognostic value of EEG regarding sedative history and various etiologies in pediatric patients who had undergone EEGs at the pediatric intensive care unit of Severance Hospital for 5 years.

Methods: We performed a retrospective study of total 113 pediatric patients who met our criteria. In-hospital mortality was measured for the primary outcome.

Results: In-hospital mortality was observed in 43 patients (38.1%) and sedatives were used in 37 patients (32.7%). Patients who showed in-hospital mortality were more like to have higher EEG background scores and absent EEG reactivity (P<0.001 for both). The prognostic values of these EEG factors were statistically significant in non-sedated patients (P<0.001 for both) whereas they were not significant in sedated patients (P=0.980 and P=0.336, respectively). In a multivariable regression analysis conducted in non-sedated patients, higher EEG background score and absence of EEG reactivity were independently associated with higher mortality rate (P=0.015 and P=0.001, respectively). They also showed high prognostic values of mortality in non-sedated patients, irrespective of each etiology (hypoxic ischemic encephalopathy [HIE]: P=0.013 and P=0.021, respectively; non-HIE structural brain disease: P=0.001 and P=0.002, respectively; non-structural brain dysfunction: P<0.001 for both).

Conclusion: Our findings prove that both an abnormal background rhythm and the absence of reactivity in early EEG can be independent factors associated with mortality in non-sedated critically ill children irrespective of etiology.

Keywords: Intensive care units, pediatric; Electroencephalography; Mortality; Prognosis; Etiology

Introduction

Predicting the prognoses of children admitted to pediatric intensive care units (PICUs) for critical care is important to both clinicians and families. Futile investigations and treatments can be avoided when a poor outcome is predicted, while more active management can be pursued with patients whose outcomes are thought to be favorable. Communication with families is also fa-
ciliated if poor outcomes are predicted at the start of patient admission to PICU. Therefore, risk factors, laboratory results, and other results from different tests, such as electrocardiography, which are thought to have prognostic values in mortality and morbidity in patients admitted to PICUs have been continuously investigated, and mortality prediction models integrating such factors have been suggested [1,2].

Electroencephalography (EEG), a non-invasive, bedside investigative tool reflecting cortical activities and dysfunction that can be readily applied to both adult and pediatric patients in intensive care units (ICUs), is also well known to have prognostic significance in critically ill patients in several studies [3-6]. EEG is a sensitive tool to detect encephalopathies, and patients with neurologic complications were shown to have an increased risk of mortality compared with patients who do not exhibit these problems [7]. However, previous studies have mostly focused on the prognostic values of EEG in adult ICU patients compared with pediatric patients, and our understanding of specific EEG findings that are associated with poor outcomes in pediatric patients is incomplete. In addition, many of these studies mainly focused on narrow etiologies such as hypoxic ischemic encephalopathy (HIE) or sepsis, rather than diverse etiologies of real ICU situations. Therefore, EEG findings that are associated with poor outcomes in pediatric patients with diverse etiologies admitted to a PICU need to be defined.

Although studies on adults have shown that continuous sedative infusions are associated with prolonged periods of mechanical ventilation and increased mortality, it is difficult to discontinue sedation in pediatric patients who are more vulnerable to self-extubation, adverse cardiovascular effects, ventilator fighting, and negative psychological effects causing frequent sedative use in critically ill children [8-10]. However, background EEG rhythms can be affected by sedatives—increased level of sedation can cause progressive slowing in basic EEG rhythms; fast activities may be more dominant upon light sedation; but increased delta activities, burst-suppression, suppression, and then isoelectric patterns are observed as sedation becomes deeper [11, 12]. Therefore, EEG background rhythms of sedated children may not have prognostic significance because the changes could be the results of sedative effects.

In this context, this study was designed to assess the prognostic value of EEG in children with newly developed neurological disorders of diverse etiologies who were admitted to the PICU, and to discover EEG findings associated with poor outcomes, such as the mortality or morbidity rate. In addition, we compared the EEG findings between the sedated and non-sedated groups to assess the relationship with intravenous sedative infusions.

Materials and Methods

1. Study design and patient selection

A retrospective study was conducted with patients who had undergone EEGs at the PICU of Severance Hospital for 5 years, from January 2012 to December 2016. The inclusion criteria were as follows: (1) patients that had EEGs performed on them within 72 hours of admission to the PICU, and (2) patients who were between the ages of 44 weeks (post-conceptual) and 18 years at the time of admission to PICU. Patients with a history of neurological disorders, epilepsy, developmental delay, or those who had a history of abnormal EEGs, were excluded to avoid complications with baseline abnormalities. Patients admitted to the neurosurgical ICU with a primary diagnosis of head trauma or those that needed neurosurgical intervention were also excluded. This study was approved by the Institutional Review Boards of Severance Hospital (4-2015-0854). We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

2. Clinical variables

In-hospital mortality was selected as a prognostic marker because it could be accurately retrieved from the past chart reviews. Mortality was assessed for each group of patients with the same EEG background scores, and the relationship between mortality and the absence of EEG reactivity was also investigated.

Clinical factors that may be associated with poor outcomes, such as gender, age at EEG recording, duration of ICU or hospital admission, time from ICU admission to EEG initiation, etiologies of ICU admission, reasons for EEG recording, and sedation history, were also collected. Scores of the pediatric risk of mortality III (PRISM III), a mortality prediction model for children admitted to PICUs, measured at the first 24 hours of PICU stay (PRISM III-24), were calculated [1].

The etiologies for PICU admission were categorized into one of the following: (1) HIE diagnosed by computed tomography or magnetic resonance imaging (MRI); (2) non-HIE structural brain disease such as encephalitis or other structural brain damage; (3) functional or non-structural brain dysfunction with no evident brain damage shown on MRI, but with a possible source of brain malfunction such as hypoxic, metabolic, toxic, or infectious etiologies; and (4) others indicating non-central nervous system (CNS) dysfunction [5].

The reasons that led to EEG evaluations in patients were labeled as follows: (1) evaluation after anoxia or hypoxia; (2) alteration in mental status; (3) presence of definite seizures; (4) suspicious movements that are unlikely to be seizures but needed fur-
ther investigation; and (5) focal neurologic signs.

The patients were then further divided into two groups, one comprising patients who received continuous intravenous infusion of sedatives or analgesics, mostly midazolam, ketamine, fentanyl, or a combination of the three drugs, and the other group consisted of patients that were not sedated at the time when their first EEGs at the PICU were taken.

3. EEGs
Scalp EEGs were performed using gold cup electrodes placed according to the international 10 to 20 system, and they were recorded using a portable video-EEG system (Telefactor, Grass Technologies, Rockland, MA, USA). EEGs were either performed for 30 minutes or monitored continuously (for a minimum of 4 hours) depending on the clinician’s judgment based on ongoing EEG results and the clinical status of the patient. EEG reactivity was checked by eye opening and closing or noise in more alert patients, or by exposure to alerting stimuli such as touch or light pain to more obtunded patients. EEG reactivity was considered present if there was a definite reproducible change in the amplitude and frequency in background activities after exposure to stimuli.

The first EEGs performed after PICU admission within 72 hours for each patient were freshly reviewed by two pediatric neurologists. The EEG backgrounds and presence of reactivity were analyzed. The EEG background scores were recorded according to a scoring system that have shown its usefulness for predicting the neurological prognosis in hypoxic encephalopathy patients, with poorer EEG backgrounds showing higher scores: (1) normal, (2) diffuse slowing (continuous EEG pattern with a dominant frequency less than that appropriate for age: < 4 Hz for < 6 months of age, < 6 Hz for < 1 year of age, and < 8 Hz for ≥ 2 years of age), (3) epileptiform (seizures and generalized periodic discharges), (4) epileptiform (seizures and generalized periodic discharges), (4) burst-suppression (clear increases in amplitude of ≥ 20 µV [bursts], followed by inter-burst intervals of at least 1 second with low-voltage activity [suppressions]), (5) low-voltage (EEG activity of < 20 µV), and (6) isoelectric (without any visible EEG activity) [13]. Next, we divided the background EEG scores into three different groups including two consecutive scores in each group to avoid small-sized patient cohorts. Examples of EEGs from our patients for each background score are demonstrated in Fig. 1. Meetings were held for mutual agreement, but disagreements in background scores and the presence of reactivity did not arise.

4. Statistical analysis
Comparisons of the two groups were performed using chi-square tests or Fisher’s exact tests for categorical or ordinal data and Mann-Whitney U tests for non-parametric continuous data. Univariate regression analysis was also used for risk analysis. To exclude any confounding factors, multivariable regression analysis was conducted. To avoid false-negative results, factors that were highly influenced by each other, such as the background EEG score and absence of EEG reactivity, were analyzed separately. A P < 0.05 was considered significant. The SPSS version 23.0 (IBM Co., Armonk, NY, USA) was used for all the analyses. Values were expressed as medians with interquartile ranges (IQRs) for continuous and ordinal variables, or as counts and percentages for categorical variables.

Results

1. Demographics
In total, 221 patients had undergone EEGs at the PICU of Severance Children’s Hospital between January 2012 and December 2016, within 72 hours of admission to the PICU. Of the 221 patients, 108 patients that had a history of neurologic disorder, delayed development, epilepsy before PICU admission, or whose previous EEG results showed abnormal findings were excluded.

The remaining 113 patients were included in this study, and their characteristics are summarized in Table 1. Among them, 65 (57.5%) were boys, and the median age when the first EEGs were performed during the PICU stay was 2.0 years (IQR, 0.5 to 6.2). The median PICU duration was 14 days (IQR, 7 to 32), and the median total hospital duration was 42 days (IQR, 22 to 86). The first EEGs of these patients at the PICU were performed at a median of 19 hours (IQR, 8 to 36) after PICU admission. Thirty-minute standard EEGs were performed in 93 patients (82.8%), and continuous EEG monitoring was performed in 20 patients (17.7%).

Patients with structural brain damage (n = 66, 58.4%), including HIE (n = 35, 31.0%) and non-HIE structural brain disease, such as encephalitis or other structural brain damage (n = 31, 27.4%), accounted for more than 50% of patients who underwent EEG at the PICU. Patients with non-structural brain dysfunction (n = 41, 36.3%) also accounted for a large proportion, mainly due to the risk of developing hypoxic encephalopathy from pulmonary diseases (n = 17, 15.0%) and developing metabolic encephalopathy due to hepatic failure (n = 15, 13.3%). Other than pulmonary and hepatic diseases, renal failure (n = 4, 3.5%) and sepsis (n = 5, 4.4%) also accounted for some proportion of non-structural brain dysfunction. Six patients (5.3%) were classified as ‘other,’ indicating non-CNS dysfunction.

Among the 113 patients, the most common reason for EEG was a hypoxic or an anoxic event (n = 40, 35.4%), followed by alteration of the mental status (n = 36, 31.9%), the presence of a sei-
zure (n = 20, 17.7%), suspicious seizure-like movements (n = 15, 13.3%), and focal neurologic signs (n = 2, 1.8%). In addition, sedatives were used before the initiation of EEG recording in 37 patients (32.7%).

2. Clinical characteristics, EEG background score, and EEG reactivity according to in-hospital mortality

Forty-three patients (38.1%) died during the hospital stay, and 70 patients (61.9%) were discharged from the hospital. Patients who showed in-hospital mortality were significantly older (P = 0.012). The length of stay at the PICU was significantly longer in patients who showed in-hospital mortality (P = 0.001), and the total length of hospital stay, including periods in the general ward after PICU discharge, was significantly longer in patients that were discharged (P = 0.037). The PRISM III-24 score was significantly higher in patients who showed mortality (P < 0.001). Both etiologies of PICU admission (P = 0.744) and sedation history (P = 0.106) were not significantly associated with mortality (Table 1).

The number of patients who showed each EEG background score was as follows: (1) normal (n = 12, 10.6%), (2) diffuse slowing (n = 45, 39.8%), (3) epileptiform (n = 9, 8.0%), (4) burst-suppression (n = 4, 3.5%), (5) low-voltage (n = 24, 21.2%), and (6) isoelectric (n = 19, 16.8%). Among them, the mortality cases were reported as 0, 9, 3, 2, 13, and 16 patients for each EEG background score, respectively, thus showing a higher mortality rate as the background EEG score increased (P < 0.001). In addition, of the 62 patients (54.9%) that showed the absence of EEG reactivity, 40 patients showed in-hospital mortality with a significant association
between these two variables \( (P < 0.001) \) (Table 1). When multivariable regression analysis was conducted to exclude confounding clinical factors, the EEG background score \( (P = 0.003) \) and absence of EEG reactivity \( (P < 0.001) \) were proven to have prognostic value for in-hospital mortality.

### Table 1. Demographics of all patients and clinical characteristics according to in-hospital mortality

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=113)</th>
<th>Yes (n=43)</th>
<th>No (n=70)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>2.0 (0.5–6.2)</td>
<td>4.8 (1.3–9.0)</td>
<td>1.2 (0.5–5.1)</td>
<td>0.012*</td>
</tr>
<tr>
<td>Male sex</td>
<td>65 (57.5)</td>
<td>24 (55.8)</td>
<td>41 (58.6)</td>
<td>0.773</td>
</tr>
<tr>
<td>IOD (day)</td>
<td>14 (7–32)</td>
<td>24 (10–55)</td>
<td>10 (6–22)</td>
<td>0.001*</td>
</tr>
<tr>
<td>HOD (day)</td>
<td>42 (22–86)</td>
<td>30 (15–58)</td>
<td>56 (25–93)</td>
<td>0.037*</td>
</tr>
<tr>
<td>Reason for undergoing EEG</td>
<td></td>
<td></td>
<td></td>
<td>0.744</td>
</tr>
<tr>
<td>After anoxia/hypoxia</td>
<td>40 (35.4)</td>
<td>17 (39.5)</td>
<td>23 (32.9)</td>
<td></td>
</tr>
<tr>
<td>Alteration in mental status</td>
<td>36 (31.9)</td>
<td>17 (39.5)</td>
<td>19 (27.1)</td>
<td></td>
</tr>
<tr>
<td>Presence of seizures</td>
<td>20 (17.7)</td>
<td>6 (14.0)</td>
<td>14 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Suspicious movements</td>
<td>15 (13.3)</td>
<td>2 (4.7)</td>
<td>13 (18.6)</td>
<td></td>
</tr>
<tr>
<td>Focal neurologic signs</td>
<td>2 (1.8)</td>
<td>1 (2.3)</td>
<td>1 (1.4)</td>
<td></td>
</tr>
<tr>
<td>PRISM III-24</td>
<td>9 (3–14)</td>
<td>12 (7–16)</td>
<td>7 (2–12)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Time from PICU admission to EEG (hr)</td>
<td>19 (8–36)</td>
<td>19 (11–40)</td>
<td>18 (7–28)</td>
<td>0.191</td>
</tr>
<tr>
<td>EEG recording duration</td>
<td></td>
<td></td>
<td></td>
<td>0.843</td>
</tr>
<tr>
<td>Standard 30 min</td>
<td>93 (82.3)</td>
<td>35 (81.4)</td>
<td>58 (82.9)</td>
<td></td>
</tr>
<tr>
<td>Continuous monitoring</td>
<td>20 (17.7)</td>
<td>8 (18.6)</td>
<td>12 (17.1)</td>
<td></td>
</tr>
<tr>
<td>EEG background score</td>
<td>2 (2–5)</td>
<td>5 (3–6)</td>
<td>2 (2–3)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Absence of EEG reactivity</td>
<td>62 (54.9)</td>
<td>40 (93.0)</td>
<td>22 (31.4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>In-hospital mortality (yes)</td>
<td>43 (38.1)</td>
<td>18 (41.9)</td>
<td>19 (27.1)</td>
<td>0.106</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or number (%). IOD, duration of PICU admission; HOD, duration of hospital admission; PICU, pediatric intensive care unit; HIE, hypoxic ischemic encephalopathy; EEG, electroencephalography; PRISM III-24, score of the pediatric risk of mortality III measured at the first 24 hours of PICU stay.

*Statistically significant clinical characteristics of critically ill patients according to in-hospital mortality.

3. Prognostic values of EEG according to sedation at the time of EEG recording

The patients were then further divided into two groups based on receiving intravenous sedative infusion at the time of EEG. Thirty-seven patients (32.7%) were sedated at the time of EEG recording. When the clinical characteristics were analyzed, the length of stay at the PICU was significantly longer in sedated patients \( (P = 0.005) \). The EEG background score was significantly higher in sedated patients \( (P = 0.012) \), and the absence of EEG reactivity was significantly higher in sedated patients \( (P < 0.001) \), thus showing that sedation indeed influences EEG background rhythms and reactivity.

Furthermore, clinical factors that are likely to influence EEG features were analyzed for their association with in-hospital mortality in each group (Table 2). In this univariate analysis, the first EEG was performed significantly late in those who showed in-hospital mortality in the sedated group \( (P = 0.027) \). In addition, patients with in-hospital mortality were significantly older \( (P = 0.049) \). However, the EEG background score and absence of EEG reactivity were not associated with in-hospital mortality in the sedated group \( (P = 0.980 \) and \( P = 0.336, \) respectively) (Fig. 2A). In the non-sedated group, the duration of PICU stay was significantly higher in patients who showed in-hospital mortality \( (P = 0.024) \). The EEG background score was significantly higher, and the absence of reactivity was significantly more frequent in patients who showed in-hospital mortality \( (P < 0.001 \) for both) (Fig. 2B). PRISM III-24 was significantly higher in patients who showed mortality in both the sedated and non-sedated groups \( (P = 0.037 \) and \( P = 0.004, \) respectively).

The odds ratio for mortality according to the EEG background
score and reactivity adjusted for variables of age at EEG recording, sex, PICU duration, hospital duration, time between PICU admission and EEG initiation, EEG recording duration (standard 30-minute recording vs. continuous monitoring), and PRISM III-24, were then calculated for non-sedated patients at the time of EEG recording (Table 3). In this multivariable analysis, a higher EEG background score showed a significantly higher mortality rate ($P = 0.015$), and the absence of EEG reactivity was also significantly associated with a higher mortality rate ($P = 0.001$).

4. Prognostic values of EEG according to the etiology of PICU admission in non-sedated patients

The prognostic values of EEG were then calculated in non-sedated patients according to the etiologies at PICU admission. In patients diagnosed with HIE, higher EEG background scores ($P = 0.013$) and the absence of EEG reactivity ($P = 0.021$) were highly associated with in-hospital mortality. Higher EEG background scores and the absence of EEG reactivity in patients with other etiologies were also observed, such as non-HIE structural brain disease ($P = 0.001$ and $P = 0.002$, respectively) and non-structural brain dysfunction ($P < 0.001$, both), thus confirming the prognostic value of EEG in various etiologies.
in children, a study by Ramachandrannair et al. [30] showed an association between the absence of EEG reactivity and increased mortality and neurologic impairment in comatose children.

In our study, a higher EEG background score and the absence of EEG reactivity from EEGs performed within 72 hours from PICU admission were associated with an increased risk of mortality after adjusting for clinical factors in non-sedated patients, a finding that is concordant with previous study findings. No mortality was found with a normal EEG; in addition, compared with patients with a normal EEG or with only diffuse slowing, patients whose EEG showed epileptiform backgrounds or burst-suppression patterns were 193.3 times more likely to die (95% confidence interval [CI], 3.4 to 10,886.1; \( P = 0.010 \)), and patients with low-voltage or isoelectric EEG were 692.6 times more likely to die (95% CI, 7.6 to 62,708.2; \( P = 0.004 \)), respectively. Patients with absent EEG reactivity were 234.1 times more likely to die than patients who showed EEG reactivity (95% CI, 9.4 to 5,831.9; \( P = 0.001 \)) (Table 2).

Changes in the EEG background rhythm and EEG reactivity with an increasing level of sedation were also demonstrated in previous reports [12,31]. In our study, sedation alone significantly influenced the EEG background and reactivity, and the EEG background score and reactivity did not predict mortality if EEG was performed in sedated patients but predicted mortality in non-sedated patients. However, in a study by Azabou et al. [4] conducted with septic adult patients in the ICU, excessive sedation was not related to the absence of EEG reactivity [11]. This discrepancy is probably due to the deeper level of sedation observed in our patients with a median Richmond agitation-sedation scale (RASS) of –4 (IQR, –3 to –4) compared with –2 in the study by Azabou et al. [4]. A deeper level of sedation is possibly associated with EEG background change and the absence of EEG reactivity [32]. Therefore, although EEG findings can be used as a prognostic factor in children in the PICU, accurate prediction of outcomes in deeply sedated patients at the time of recording may be difficult.

EEGs in patients with HIE, which often accompanies neuronal deaths, have been demonstrated to be more useful in predicting prognoses compared with those in patients receiving critical care with other etiologies [3]. There is limited literature on the relationship between the EEG background and clinical outcome in critically ill patients with etiologies other than HIE, and even fewer in children in the PICU. However, neurologic complications commonly occur in critically ill children without a definite history of anoxia. In addition, in our study comprising patients admitted to the PICU with various reasons, the EEG background rhythm showed an association with mortality, suggesting that EEG is
more widely applicable to diverse patient populations.

This study is significant because it is the first study to our knowledge, to investigate the relationship between early EEG findings and mortality outcomes in critically ill children with diverse etiologies, irrespective of the comatose status, as well as the association with sedatives.

However, this study has several limitations. Due to its retrospective nature, the depth of sedation at the exact time of EEG recording was not retrieved. Instead, the RASS scores charted every 8 hours closest to the time of EEG recording were collected. Therefore, changes in the EEG background rhythm and reactivity according to the depth of sedation could not be assessed. In addition, because 82.3% of patients underwent standard 30-minute EEG while only 17.7% of patients were studied with continuous EEG monitoring, seizure burdens that could affect the prognosis in critically ill children could not have been assessed [33]. The trends and changes in the EEG background rhythms over time is also another prognostic factor, but this also could not be analyzed [34,35]. Finally, univariate and multivariable regression analysis could not be performed in non-sedated patients with each different etiologies because of the small-sized cohort.

In conclusion, abnormal background rhythms and absent reactivity in early EEG can be an independent predictor for mortality in non-sedated critically ill children in the PICU, irrespective of the etiology.

Conflicts of interest

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

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References


The Risk Factors and Clinical Features of Posttraumatic Seizure in Preschool-Aged Children

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Introduction

Childhood head trauma is a major cause of death and disability. In the United States, the incidence of head trauma in childhood has increased steadily over the last decade, with more prevalence among children under 4 years of age [1]. In Korea, 55% of head trauma in children under 18 years old occurred in 0 to 4 years old [2]. Posttraumatic seizure (PTS) is complication that occur in patients with head trauma, which is classified according to the latency, immediate seizures within 24 hours after trauma, early seizures within 7 days, and late seizures after 7 days. The overall incidence of PTS in children is 5% to 10% [3-5], and the incidence of PTS in severe traumatic brain injury (TBI) is 10 times higher than in mild TBI [6,7]. Risk factors associated with the PTS include skull fracture, brain parenchymal hemorrhage, focal neurologic deficit at admission, duration of unconsciousness over 24 hours, extensive brain contusion, low Glasgow Coma Scale (GCS) score, abnormal findings in brain computed tomography (CT) scan, and...
age of 2 years or less [8-13]. Although there were many studies about PTS in children of various ages, there is a lack of research on the clinical characteristics and risk factors of PTS in preschool-aged children.

The purpose of this study was to investigate the incidence, clinical features, and risk factors of PTS in preschool-aged children with head trauma.

Materials and Methods

1. Patients selection

From January 2011 to December 2015, total 1,578 patients under 6 years of age visited the emergency department or outpatient clinic of Wonju Severance Christian Hospital due to head trauma. Two patients were excluded due to insufficient medical records and 1,576 patients were enrolled in this retrospective study.

2. Definitions

Head trauma is defined as any physical injury to the head. And TBI is defined as a disruption in the normal function of the brain that can be caused by a bump, blow, or jolt to the head or a penetrating head injury [14]. In this study, the causes of the accident were classified into fall down injury, slip down injury, blunt trauma, passenger traffic accident, pedestrian traffic accident and cause unknown. Altered brain function was confirmed by thorough neurologic examination, checking alteration of consciousness, GCS score, focal neurologic deficit. In this study, patients with GCS score 13 to 15 were classified as mild TBI, GCS 9 to 12 as moderate TBI, GCS < 8 as severe TBI [15]. PTS are the types of seizures that arise from TBI due to physical trauma [16]. PTSs are commonly derived into three classes by latency; immediate seizures, early seizures, and late seizures. Immediate seizures refer to PTSs that happen at or minutes after impact; PTSs that occur one week after head injury are called early seizures, and late PTSs are defined as those occurring 1 week after injury [12,17,18]. Skull X-rays and brain CT scans were performed if indicated according to Pediatric Emergency Care Applied Research Network (PECARN) rule or if parents wanted.

3. Statistical analysis

The characteristics of the patients with and without seizures were compared by t-test at age and chi-square test at the other variables. Cells with an expected frequency of 5 or less were compared using Fisher’s exact test. Chi-square test was used to compare the incidence of generalized seizures, and the Kruskal-Wallis test was used to compare the mean latency and duration of seizures. If P value was less than 0.05, it was judged to be statistically significant, and SPSS version 23.0 (IBM Co., Armonk, NY, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) were used.

4. Ethics

It was conducted in accordance with ethical standards in accordance with the “Medical Ethics Guidelines” and was approved by the Institutional Review Board (CR318094). Informed consent was waived due to the retrospective nature of the study.

Results

1. Characteristics of head trauma and demographics

Among the patients with head trauma, 955 (60.6%) were males and 621 (39.4%) were females. The male to female ratio was 1.54:1 and the mean age was 2.02 years. The incidence of head trauma was 388 (24.6%) at 1-year-old, 340 (21.6%) at 0-year-old, 264 (16.8%) at 2-year-old, 203 (12.9%) at 4-year-old, and 155 (9.8%) at 5-year-old by age. PTS occurred in 53 patients (3.36%) (Table 1).

2. Clinical characteristics of post-traumatic seizures

Among the patients with PTS, 17 (32.1%) were immediate seizures, six (11.3%) were early seizures, and 30 (56.6%) were late seizures. The median latency was 0 hours (range, 0 to 8) in immediate seizure, median 2.5 days (range, 2 to 5) in early seizure, and median 197 days (range, 10 to 2,038) in late seizure. Generalized seizure was observed in 20 patients, which was 23.5% in immediate seizures, 50.0% in early seizures, and 43.3% in late seizures. The duration of seizure was 185.0 ± 162.5 seconds in immediate seizure, 570 ± 927.0 seconds in early seizure, and 215.4 ± 186.5 seconds in late seizure (P = 0.796) (Table 2).

3. Risk factors of post-traumatic seizures

At the time of admission, body temperature was measured in 1,447 patients, and 38 patients (2.6%) had fever over 38.0°C. Nine of 38 patients (23.7%) with fever, and 38 of 1,409 patients (2.7%) without fever experienced PTS (odds ratio [OR], 11.20; P < 0.001). There was a history of seizures in 45 of patients (2.86%) with head trauma, and 10 of them (22.2%) had PTS, while only 43 of 1,531 patients (2.8%) without history of seizures had PTS (OR, 9.22; P < 0.001). The causes of head trauma were in the order of blunt trauma (34.5%), fall down injury (29.5%), slip down injury (25.1%), passenger traffic accident (7.2%), pedestrian traffic accident (1.9%). The incidence of PTS was highest (4.8%) in slip down injury (P = 0.27). According to the TBI severity by GCS scores, 1,561 patients (99.0%) had mild TBI, seven patients (0.4%) had moderate TBI, and eight patients...
Table 1. Comparison of clinical characteristics between seizure and non-seizure group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=1,576)</th>
<th>With seizure (n=53)</th>
<th>Without seizure (n=1,523)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>2.02±1.63</td>
<td>1.68±1.48</td>
<td>2.03±1.63</td>
<td>0.123</td>
</tr>
<tr>
<td>0</td>
<td>340 (21.6)</td>
<td>11 (3.2)</td>
<td>329 (96.8)</td>
<td>0.309</td>
</tr>
<tr>
<td>1</td>
<td>388 (24.6)</td>
<td>20 (5.2)</td>
<td>368 (94.8)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>264 (16.8)</td>
<td>8 (3.0)</td>
<td>256 (97.0)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>226 (14.3)</td>
<td>7 (3.1)</td>
<td>219 (96.9)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>203 (12.9)</td>
<td>3 (1.5)</td>
<td>200 (98.5)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>155 (9.8)</td>
<td>4 (2.6)</td>
<td>151 (97.4)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.800</td>
</tr>
<tr>
<td>Male</td>
<td>955 (6.06)</td>
<td>33 (3.5)</td>
<td>922 (96.5)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>621 (39.4)</td>
<td>20 (3.2)</td>
<td>601 (96.8)</td>
<td></td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;38.0</td>
<td>38 (2.6)</td>
<td>9 (23.7)</td>
<td>29 (76.3)</td>
<td></td>
</tr>
<tr>
<td>≤38.0</td>
<td>1,409 (97.4)</td>
<td>38 (2.7)</td>
<td>1,371 (97.3)</td>
<td></td>
</tr>
<tr>
<td>History of seizure</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>With history</td>
<td>45 (2.9)</td>
<td>10 (22.2)</td>
<td>35 (77.8)</td>
<td></td>
</tr>
<tr>
<td>Without history</td>
<td>1,531 (97.1)</td>
<td>43 (2.8)</td>
<td>1,488 (97.2)</td>
<td></td>
</tr>
<tr>
<td>Causes of trauma</td>
<td></td>
<td></td>
<td></td>
<td>0.274</td>
</tr>
<tr>
<td>Fall down</td>
<td>465 (29.5)</td>
<td>11 (2.4)</td>
<td>454 (97.6)</td>
<td></td>
</tr>
<tr>
<td>Slip down</td>
<td>396 (25.1)</td>
<td>19 (4.8)</td>
<td>377 (95.2)</td>
<td></td>
</tr>
<tr>
<td>Blunt trauma</td>
<td>544 (34.5)</td>
<td>17 (3.1)</td>
<td>527 (96.9)</td>
<td></td>
</tr>
<tr>
<td>In car TA</td>
<td>113 (7.2)</td>
<td>3 (2.7)</td>
<td>110 (97.3)</td>
<td></td>
</tr>
<tr>
<td>Out car TA</td>
<td>30 (1.9)</td>
<td>1 (3.3)</td>
<td>29 (96.7)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>28 (1.8)</td>
<td>2 (7.1)</td>
<td>26 (92.9)</td>
<td></td>
</tr>
<tr>
<td>TBI severity (by GCS)</td>
<td></td>
<td></td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>Mild (13–15)</td>
<td>1,561 (99.0)</td>
<td>50 (3.2)</td>
<td>1,511 (96.8)</td>
<td></td>
</tr>
<tr>
<td>Moderate (9–12)</td>
<td>7 (0.4)</td>
<td>1 (14.3)</td>
<td>6 (85.7)</td>
<td></td>
</tr>
<tr>
<td>Severe (3–8)</td>
<td>8 (0.5)</td>
<td>2 (25.0)</td>
<td>6 (75.0)</td>
<td></td>
</tr>
<tr>
<td>Radiologic findings</td>
<td></td>
<td></td>
<td></td>
<td>0.358</td>
</tr>
<tr>
<td>Normal</td>
<td>1,396 (88.6)</td>
<td>46 (3.3)</td>
<td>1,350 (96.7)</td>
<td></td>
</tr>
<tr>
<td>Skull fracture</td>
<td>94 (6.0)</td>
<td>2 (2.1)</td>
<td>92 (97.9)</td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>44 (2.8)</td>
<td>3 (6.8)</td>
<td>41 (93.2)</td>
<td></td>
</tr>
<tr>
<td>Skull fracture&amp;ICH</td>
<td>42 (2.7)</td>
<td>2 (4.8)</td>
<td>40 (95.2)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%).
TA, traffic accident; TBI, traumatic brain injury; GCS, Glasgow Coma Scale; ICH, intracranial hemorrhage.

Table 2. Characteristics of immediate, early, and late posttraumatic seizure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Immediate</th>
<th>Early</th>
<th>Late</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval (from head trauma to seizure occurrence) (day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>214.9±436.8</td>
<td>0±0</td>
<td>3.0±1.3</td>
<td>449.8±514.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (range)</td>
<td>18 (0–2,038)</td>
<td>0 (0–0)</td>
<td>2.5 (2–5)</td>
<td>197 (10–2,038)</td>
<td></td>
</tr>
<tr>
<td>Character of seizure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.235</td>
</tr>
<tr>
<td>Generalized convulsive</td>
<td>20 (37.7)</td>
<td>4 (20.0)</td>
<td>3 (15.0)</td>
<td>13 (65.0)</td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>33 (62.3)</td>
<td>14 (42.4)</td>
<td>3 (9.1)</td>
<td>16 (48.5)</td>
<td></td>
</tr>
<tr>
<td>Duration of seizure (sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.796</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>250.9±365.79</td>
<td>185.0±162.5</td>
<td>570.8±927.0</td>
<td>215.4±186.5</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>180 (5–2,400)</td>
<td>150 (20–600)</td>
<td>195 (5–2,400)</td>
<td>180 (10–600)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%) unless otherwise indicated.
SD, standard deviation.
Because the current definition of PTS is not clear about the

history of fever, previous seizures or epilepsy, discussions about

more clear definition will be needed in the future.

The latency of PTS is known as an average of 2 years, and in the
case of early seizure, 25% of the cases appear within 1 hour after
trauma and 50% of the cases occur within 24 hours after trauma

[4,6,20,21]. In this study, the overall latency was average of 7.2
months, with an average of 1 hour in immediate seizure, 3.0 days
in early seizure, and 15.0 months in late seizure.

According to Youn et al. [19], 82.9% of generalized seizures,
17.1% of partial seizures, and 2.4% of status epileptics were ob-
served in early PTS, while 76.5% of generalized seizures and
23.5% of partial seizures were observed in late PTS. However in
this study, 28.6% of generalized seizures were observed in imme-
diate PTS patients, 50.0% in early PTS, and 44.8% in late PTS. It
is known that in posttraumatic epilepsy patients, the seizure usu-
ally occurs in the mesial temporal lobe or frontal lobe, and not fre-
quently from occipital or parietal lobe [22]. Although PTS can
occur in all forms, most early PTS show a pattern of generalized
 tonic-clonic seizures [23], about two-thirds of late PTS show gen-
eralized seizures or partial seizure with secondary generalization

[24-28]. In this study, the incidence of generalized or partial sei-
zuers was analyzed but it was not analyzed for more detailed ap-
pearance of seizures, presence of secondary generalization, the re-
lationship between PTS and electroencephalography (EEG) or
radiologic findings, so further analysis will be needed.

Mean duration of PTS was 4.2 minutes, which was 3.1 minutes
for immediate PTS, 9.5 minutes for early PTS, and 3.6 minutes for
late seizure. The duration was the longest in early PTS group ex-
cept immediate seizure, but the duration of PTS in children has not
been studied yet.

This study was the first which analyzed the risk factors of PTS

Discussion

It is known that PTSs occur in 5% to 10% of children, and the in-
cidence recently reported in Korea was 12.3%, among which early
seizure was 70.7% and late seizure was 29.3% [19]. It has been re-
ported that about 60% of early seizures develop immediately
within 24 hours after head trauma [3], which is called ‘immediate
seizure.’ In this study, PTS occurred 3.36% in preschool-aged chil-
dren, among them, 43.4% of early seizures and 56.6% of late sei-
zuers occurred and 73.9% of early seizures showed immediate sei-
zuers. In previous studies, the study group was set up as an inpa-
tient rather than an emergency room or an outpatient. In this
study, however, the incidence may have been lowered because the
number of patients who discharged was included in the study pop-
ulation. According to Asikainen et al. [5], the risk of early PTS
is high in children younger than 7 years and the risk of late PTS is
high in adolescents and adults, but in this study, the incidence of
late seizures was higher than early seizures in children under 6
years of age. This conflicting result is likely to be from the differ-
ence in inclusion criteria. In this study, patients with seizure with
fever, with previous history of seizure attack, with a history of epi-
lepsy were all included while most of previous studies excluded
them. Because the current definition of PTS is not clear about the

(0.5%) had severe TBI. The incidence of PTS was 3.2% in mild
TBI, 14.3% in moderate TBI, and 25.0% in severe TBI

(P = 0.012) (Fig. 1). Skull X-ray and brain CT scan results were
normal in 1,396 (88.6%), skull fracture in 94 (6.0%), intracranial
hemorrhage (ICH) in four (2.8%), concurrent skull fracture and
ICH in 42 (2.7%), and it was not correlated with the incidence of
seizures (P = 0.40) (Table 1 and Fig. 2).

Fig. 1. Seizure incidence by traumatic brain injury (TBI) severity.

Fig. 2. Seizure incidence by radiologic findings. ICH, intracranial
hemorrhage.
in preschool-aged children, under 6 years. In this study, the risk factors for PTS were fever over 38.0°C at the time of head trauma, history of seizure, and low GCS score at visit. However, age, sex, cause of head trauma, and radiologic findings were not associated with PTS. Because there is little known about the relationship between fever and PTS, it is noteworthy that fever was identified as a risk factor for PTS, especially considering that fever is frequently observed in preschool-aged children. Seizures with fever after head trauma may be difficult to distinguish from febrile seizures, which are common in this age group. Therefore, additional studies such as EEG, brain imaging modalities, and close follow-up are necessary.

Previous studies have shown that low GCS score in head trauma patients is a poor prognostic factor for TBI and is a risk factor for PTS [29-31]. Thapa et al. [32] reported that the risk of PTS in severe TBI increased about four times in patients with a GCS score of less than 9, compared to patients with a GCS score of 14 to 15. Similarly, in this study, the risk of PTS was 7.8 times higher in patients with severe TBI compared to mild TBI.

In children less than 2 years of age, the skull is thin due to its anatomical structure and it is vulnerable to fractures. In addition, the subarachnoid space is narrow so that TBI risk increases. For these reasons, PTS in this age group is relatively common, especially early PTS [33-35]. In this study, PTS occurred most frequently at 1 year of age (5.2%), but it was not significant.

In this study, 60.6% of the patients with head trauma were male and there was no difference in incidence of PTS according to sex, same as our previous study [36].

The causes of childhood head trauma in Korea during the last 10 years are as follows. For children under 2 years of age in 2007, 47.4% of fall down injury, 19% of crash injury, 9.5% of traffic accidents were reported [37], and for preschool-aged children in 2015, 71.4% of fall down injury, 22.1% of crash injury, 6.5% of traffic accident were reported [36]. And in this study, the causes of head trauma in children under 6 year of age were 34.5% of blunt trauma, 29.5% of fall down injury, 25.1% of slip down injury, 7.1% of passenger traffic accident, 1.9% of pedestrian traffic accident, and 1.8% of unknown cause. Because ‘blunt trauma’ and ‘slip down injury’ are type of collision, it may be thought that fall down injuries has been decreased while injury by collision has increased recently.

Kim et al. [38] reported 63.2% of cerebral concussion and 45.6% of skull fracture in children under 2 years of age according to radiologic findings. Kim et al. [39] reported that 83.8% of PTS patients under 18 years of age had radiographic abnormalities, of which 51.6% had brain parenchymal hemorrhage and 45.1% had ICH. In this study, radiologic diagnosis of head trauma patients under the age of 6 years was similar to that of the previous study in the order of brain contusion (88.6%), skull fracture (8.8%), ICH (5.5%).

The purpose of this study was to investigate the incidence, clinical features and risk factors of PTS in children under 6 years old. It is the largest study in Korea, and has identified some interesting results presented above, but it has some limitations. First, because it was a retrospective study based on medical records, there was a limitation in getting more detail history of head trauma, associated symptoms and in evaluation of TBI severity. Also we could not analyze the prognosis because of the lack of long-term follow-up. Second, because the results of this study are based on data collected from a single institution in a city, it is difficult to generalize these results as the clinical features of head injury and PTS in preschool-aged children in Korea. In the future, a randomized controlled trial in larger population is needed to know the clinical characteristics, risk factors, and the prognosis of pediatric head trauma and PTS in Korea.

Conflicts of interest

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

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References

36. Na YH, Koh ID, Cha BH. The risk factors of brain injury by head trauma in preschool aged children. J Korean Child Neu-
Mononeuropathy is rare among children. Deymeer and Jones [1] reported that 6% of children (78 out of 1,319) referred to their pediatric electromyography (EMG) laboratory within an 11-year-period (1979 to 1990) were diagnosed with mononeuropathy, and 17 patients were diagnosed with pediatric median mononeuropathy over 14 years (1979 to 1994). A more recent paper from Davis and Vedanarayanan [2] reported their experience diagnosing 13 pediatric patients with carpal tunnel syndrome, or median neuropathy at the wrist, within an 11-year-period, from 1,800 children who underwent EMG-nerve conduction study (NCS). Carpal tunnel syndrome is a clinical syndrome where the patient experiences a multitude of symptoms including tingling or numbness of the hand, pain in hand, wrist, or forearm, and reduced grip strength, believed to be caused by compression of the median nerve in the carpal tunnel [3]. Causes of carpal tunnel syndrome in pediatric patients include lysosomal storage diseases like: mucopolysaccharidosis and mucolipidosis, congenital bone anomalies, hypothyroidism, or myopathic contractures [4].

A previously healthy 33-month-old girl came to the hospital complaining of weakness in her right hand. Her mother noticed the weakness a week prior when she held the patient’s hand while walking. In some photos taken of her at daycare, it was identified that the patient had transitioned to primary usage of her left hand, despite her right-handedness; suggesting that symptoms, like weakness, may have been prevalent before the prior week. When asked by clinicians, the patient denied symptoms of weaknesses in other parts of her body. She was unable to use her left hand properly, suggesting her having pathological left-handedness was less likely. No history of trauma or recent infections was found, rather, the patient had been in good condition, sleeping and eating well. Her immunization records were up-to-date and development normal. She didn’t receive vaccination recently.

A physical examination at the time of admission revealed weakness of the right hand. She was unable to grasp and perform thumb opposition motions. The resulting motor grades for her thumb, second finger, and third finger were rated as grade I, and her fourth and fifth finger were rated as grade V, whereas the motor strengths of all other extremities were reported normal. Sensitivity to pain was not impaired in either hand, although other sensory testing was limited due to her age. Reflex testing revealed normal for bilateral biceps, brachioradialis and triceps deep
tendon reflexes, and Babinski reflex was negative. Other physical examinations were unremarkable.

Simple radiograph imaging was performed on her bilateral forearm and revealed no significant bony abnormalities. NCS of the right arm generated a normal response for both the sensory and motor components in the right median and ulnar nerves, although F-waves were not observed when stimulating the right median nerve. Magnetic resonance imaging (MRI) of the right wrist with contrast enhancement showed diffuse T2 signal alterations, with swelling of the distal median nerve from distal radius level, and no evidence of extrinsic nerve compression in the covered range. This suggests a median nerve neuropathy of inflammatory origin. Furthermore, increased T2 signal intensity in the pronator quadratus, abductor pollicis brevis, flexor pollicis brevis, opponens pollicis, and 1st, 2nd, and 3rd lumbricals muscles was observed without any definite atrophic changes, suggesting acute denervation changes of the median nerve.

Diagnosis of idiopathic median nerve mononeuropathy was established given the absence of both trauma history and evidence of extrinsic nerve compression. She received steroid pulse therapy with intravenous methylprednisolone (30 mg/kg/day) for 3 days. There were no reported side effects and weakness improved on the 4th day of treatment. She was discharged the following day and followed up on at an outpatient clinic a week later. During the outpatient visit, motor strengths of all digits of her right hand were rated grade V, and she showed no other symptoms. (Fig. 1).

Even though the terms carpal tunnel syndrome and median mononeuropathy in children are used interchangeably in much of the literature, carpal tunnel syndrome is a specific form of median nerve mononeuropathy, which affects the distal portion of median nerve and is caused by increased pressure on the carpal tunnel. Causes of carpal tunnel syndrome are in most cases unknown, and suspected risk factors include diabetes mellitus, hypothyroidism, obesity, and arthritis [3].

Anatomically, the distal median nerve was involved in this case; however, MRI indicated no evidence of extrinsic nerve compression, making a carpal tunnel syndrome diagnosis unlikely. Since there was no history of infection or any preceding trauma, the pa-

![Fig. 1. Magnetic resonance imaging T2 fat saturated sequence with contrast enhancement of left wrist showing (A) swelling of the distal median nerve (arrow) and (B) increased T2 signal intensity in the pronator quadratus (arrowheads), and (C, D) abnormal T2 hyperintensity without definite atrophic changes on thenar muscles (arrow and arrowheads).](https://doi.org/10.26815/acn.2019.00031)
tient was diagnosed with idiopathic pediatric median mononeuropathy.

In contrast to carpal tunnel syndrome, where sensory symptoms such as numbness, tingling, burning, or pain are considered to be characteristic symptoms, the patient’s chief complaint was weakness of her right hand. Since the patient appeared to be irritated until she was with methylprednisone pulse therapy, this makes it hard to rule out the possibility of her not being able to express her sensory symptoms. A pediatric patient’s inability to effectively communicate their symptoms decreases pediatricians’ ability to detect rare conditions that benefit from early detection and appropriate management.

Traditionally, the gold standard for diagnosing median mononeuropathy is NCS. The sensitivity and specificity of NCSs of carpal tunnel syndrome patients vary from 75% to 96.7% depending on the study [5]. Since these studies are based on patient data from an adult population, there are clear limitations to extrapolating the results found in these studies to pediatric cases. With technological improvements to MRI technology, MRIs are used increasingly for diagnosing carpal tunnel syndrome, especially to elucidate any anatomical abnormalities. In this case, NCS failed to reveal any abnormalities in the patient’s median nerve. This may have been a false negative due to the acute nature of the illness. However, a MRI of the wrist revealed evidence of median nerve neuropathy. Currently, there is no research that directly compares the sensitivity and specificity of MRI and NCS examinations as a means of diagnosing neuropathies, but as shown by this case, an MRI might be a useful tool for diagnosing neuropathies more than has been previously reported.

In summary, this case represents a pediatric patient with idiopathic mononeuropathy of the median nerve and who was diagnosed with clinical features and imaging studies (standard X-ray and MRI), and responded well to methylprednisone pulse therapy. This study was conducted with verbal informed consent from her parents.

Conflicts of interest

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

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References

Instructions to authors

Enacted: January 31, 2019

General information

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

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All submitted manuscripts should be original and should not be in consideration by other scientific journals for publication. Any part of the accepted manuscript should not be duplicated in any other scientific journal without the permission of the Editorial Board, although the figures and tables can be used freely if the original source is verified according to Creative Commons license. It is mandatory for all authors to resolve any copyright issues when citing a figure or table from other journal that is not open access.

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3. Secondary publication

It is possible to republish manuscripts if the manuscripts satisfy the condition of secondary publication of the Recommendations from ICMJE. These are:

- The authors have received approval from the editors of both journals (the editor concerned with the secondary publication must have access to the primary version).
- The priority for the primary publication is respected by a publication interval negotiated by editors of both journals and the authors.
- The paper for secondary publication is intended for a different group of readers; an abbreviated version could be sufficient.
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The corresponding author must inform the editor of any potential conflicts of interest that could influence the authors’ interpretation of the data. Conflict of interest exists when an author or the author’s institution, reviewer, or editor has financial or personal relationships that inappropriately influence or bias his or her actions. Such relationships are also known as dual commitments, competing interests, or competing loyalties. These relationships vary from being negligible to having great potential for influencing judgment. Not all relationships represent true conflict of interest. On the other hand, the potential for conflict of interest can exist regardless of whether an individual believes that the relationship affects his or her scientific judgment. Financial relationships such as employment, consultancies, stock ownership, honoraria, and paid expert testimony are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, or of the science itself. Conflicts can occur for other reasons as well, such as personal relationships, academic competition, and intellectual passion (http://www.icmje.org/conflicts-of-interest/). If there are any conflicts of interest, authors should disclose them in the manuscript. The conflicts of interest may occur during the research process as well; however, it is important to provide disclosure. If there is a disclosure, editors, reviewers, and reader can approach the manuscript after understanding the situation and background for the completed research.

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Clinical research should be conducted in accordance with the WMA Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/). Clinical
studies that do not meet the Helsinki Declaration will not be considered for publication. For publication, the human subjects’ identifiable information, such as the patients’ names, initials, hospital numbers, dates of birth, or other protected healthcare information should not be disclosed. For animal subjects, the research should be performed based on the National or Institutional Guide for the Care and Use of Laboratory Animals, and the ethical treatment of all experimental animals should be maintained.

6. Statement of informed consent and institutional review board approval
Copies of written informed consents should be kept for studies on human subjects. For the clinical studies with human subjects, there should be a certificate, an agreement, or the approval by the Institutional Review Board (IRB) of the author’s affiliated institution. If necessary, the editor or reviewers may request copies of these documents to resolve questions about IRB approval and study conduct. In addition, for studies conducted with human subjects, the method by which informed consent was obtained from the participants also needs to be stated in the Methods section.

7. Registration of the clinical trial research
It is recommended that any research that deals with a clinical trial be registered with a primary national clinical trial registration site, such as http://cris.nih.go.kr, or other sites accredited by the World Health Organization as listed at http://www.who.int/ictrp/en/ or ClinicalTrial.gov (https://clinicaltrials.gov), a service of the US National Institutes of Health.

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The editorial board will continuously work to monitor and safeguard publication ethics: guidelines for retracting articles; maintaining the integrity of academic records; precluding business needs from compromising intellectual and ethical standards; publishing corrections, clarifications, retractions, and apologies when needed; and excluding plagiarism and fraudulent data. The editors maintain the following responsibilities: to reject and accept articles; to avoid any conflict of interest with respect to articles they reject or accept; to promote publication of corrections or retractions when errors are found; and to preserve the anonymity of reviewers.

10. Data Sharing statement

Copyrights/Open Access/Deposit/Archiving policy

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All manuscripts are initially reviewed by a Annals of Child Neurology editor. Submissions that are clearly outside the scope of Annals of Child Neurology will be declined without further review. Manuscripts that are so poorly written or incomplete that it hampers the review process will also be declined but with the option of resubmission if the concerns have been addressed. All submitted manuscripts are analyzed with plagiarism detection software prior to undergoing editorial review. Manuscripts are sent to the two most relevant investigators available for review of the contents. The editor selects peer referees by recommendation of Annals of Child Neurology’s editorial board members or from the Board’s specialist database.

The journal uses a single-blind peer review process: peer reviewer identities are kept confidential (unless reviewers choose to reveal their names in their formal reviews); author identities are made known to reviewers. The existence of a manuscript under review is not revealed to anyone other than peer reviewers and editorial staff. Peer reviewers are required to maintain confidentiality about the manuscripts they review and must not divulge any information about a specific manuscript or its content to any third party without prior permission from the journal editors. Information from submitted manuscripts may be systematically collected and analyzed as part of research to improve the quality of the editorial or peer review process. Identifying information remains confidential. Final decisions regarding manuscript publication are made by an editor who does not have any relevant conflicts of interest. All correspondence, including the editor’s decision and requests for revisions, will be conducted by e-mail.

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

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

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Manuscript preparation

1. General principles

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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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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. Abstracts of letters to editor may have an unstructured format with the same restriction on word count. 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 materials and study design should be presented in detail. In experimental research, methods should be described in such a manner that the experiments can be reproduced by the readers. The sources of special chemicals or preparations should be given (name of company, city and state, and country). Clinical studies or experiments using laboratory animals or pathogens should include approval of the studies by relevant committees. A statement concerning IRB approval and consent procedures must be presented.

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

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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.

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Examples of reference styles

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

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Tables
1) Each table should be inserted on a separate page, with the table number, table title and legend.
2) The numbers of tables should be in Arabic numerals in their order of citation.
3) Titles of tables should be concise using a phrase or a clause. The first character should be capitalized.
4) Tables should be concise and not duplicate information found in figures.
5) The significance of results should be indicated by appropriate statistical analysis.
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7) All symbols and abbreviations should be described below the table.
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All other types of manuscripts should meet the above mentioned requirements.

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

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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 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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Author's checklist

1. General provisions
☐ The authors should ensure that the contents of the present manuscript have not been published nor intended to be published in other journals.
☐ The manuscript should be formatted as follows: A4 paper, 12 point font, left-aligned, double-spaced.
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☐ References should be numbered in Arabic numbers in the order they are cited.
☐ Superscript numbers should come after commas and periods according to submission rules.
☐ When using abbreviations, their full forms should be used at first mention; abbreviations/acronyms should then be used consistently in further occurrences.
☐ Units of measure should be written in accordance with submission rules (except for % and °C, a space should come between the number and the unit of measure).
☐ For numbers, a comma should be inserted after every third digit.
☐ All statistical methods used should be described accurately in detail.

5. References
☐ In-text citations should be numbered and should correspond to the numbers in the references.
☐ Up to six authors should be mentioned. In case there are seven or more authors, “et al.” must come after the primary author.
☐ Official abbreviations of quoted journals must be used.
☐ Year, volume, and start page–end page of the quoted literature should be accurately mentioned.
☐ The first letter of the title of the quoted article should be capitalized.
☐ Compliance with quotation styles should be observed.
☐ The manuscript should comply with quotation rules in case a book has separate authors by chapter.

6. Table
☐ Each table must have its own title and be given a separate page.
☐ All abbreviations used in the table should be spelled out.
☐ All superscript numbers used in the table should comply with the contribution rules.

7. Figures
☐ Each figure should be produced in a separate file and should not be included in the main text.
☐ The file name of each figure should be the figure number.
☐ Figures can be black and white or in color; they will be published as submitted.
☐ The titles and legends of the figures should be concisely drafted on a separate page in English.
☐ The figures should be explained in complete sentences, not phrases or clauses.
☐ All abbreviations should be written out.
☐ When a figure contains several pictures, the explanation of the figure should be followed by that of each picture, distinguishing them as A, B, C, etc.