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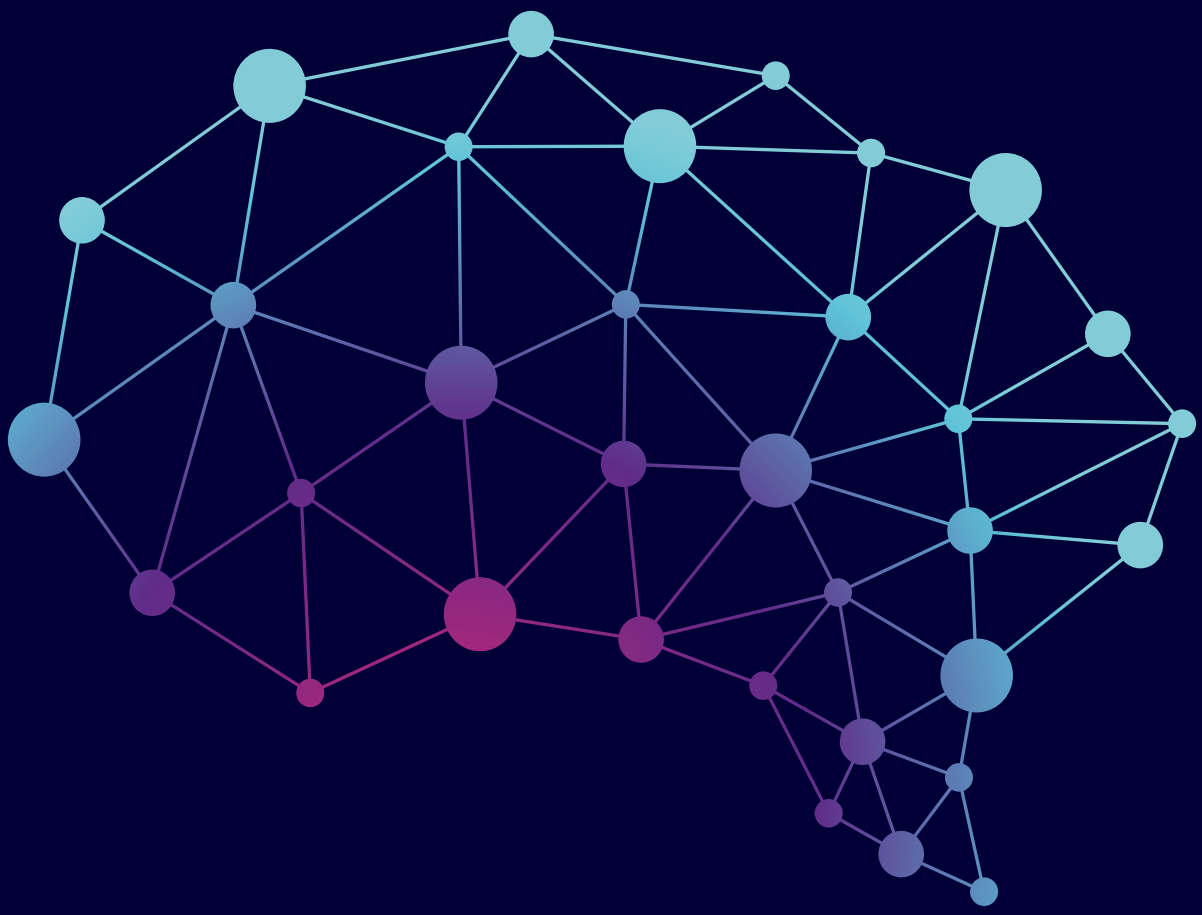

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Aims and scope

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, neuroimaging, neuromuscular medicine, neuroimmunology and inflammation, neuro-oncology, sleep medicine, vascular neurology, as well as other diseases affecting the developing nervous system.

Acceptance for publication of submitted manuscript is determined by the editors and peer reviewers, who are experts in their specific fields of pediatric neurology. The journal includes the following sections: original articles, 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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ANNALS OF CHILD NEUROLOGY

Editorial

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Annals of Child Neurology: Marking a New Path

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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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ANNALS OF CHILD NEUROLOGY

Review article

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Frequently Identified Genetic Developmental and Epileptic Encephalopathy: A Review Focusing on Precision Medicine

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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 Δ-1-piperideine-6 carboxylate (Δ1-P6C) [4]. The accumulated Δ1-P6C sequesters

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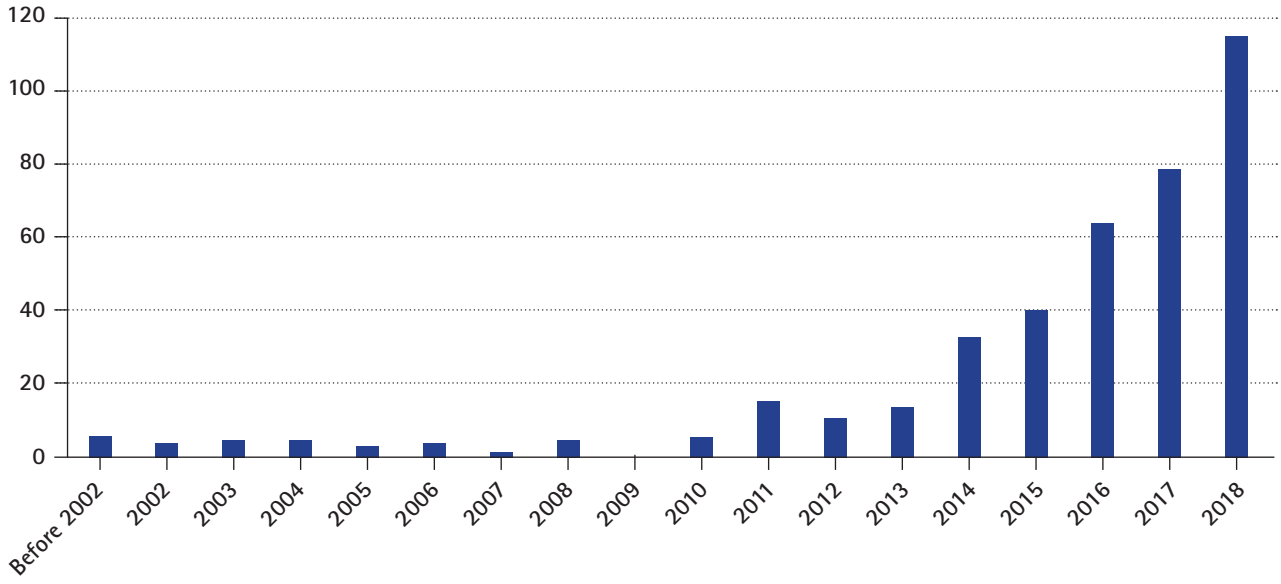

Fig. 1. Number of publications on PubMed to search terms epilepsy, and personalized or precision medicine.

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 hypsarrhythmia, 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]. In CDKL5 encephalopathy

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-iso-xazole 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

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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 KCNT1, 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 $Na_V1.2$, one of four sodium channel paralogs expressed throughout the central nervous system, along with $Na_V1.1$ (*SCN1A*), $Na_V1.3$ (*SCN3A*), and $Na_V1.6$ (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 $Na_V1.2$ 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 $Na_V1.2$ 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].

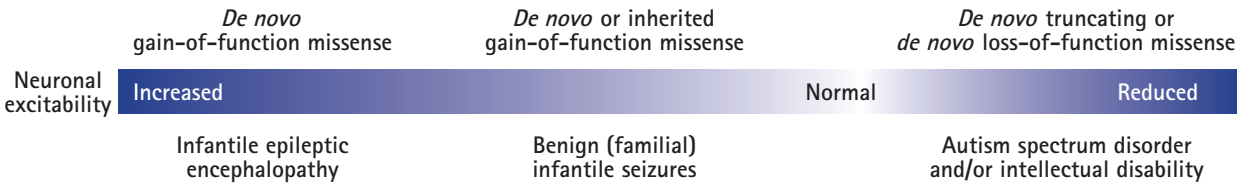

Fig. 2. Model of sodium channel, voltage-gated, type II, alpha subunit (SCN2A) encephalopathy pathophysiology. Adapted from Sanders et al. [61], with permission from Elsevier.

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 $Na_V1.1$ channels affected in Dravet syndrome are more commonly expressed in inhibitory neurons, and that loss-of-function of $Na_V1.1$ may have opposing effects in brain networks compared with $Na_V1.2$ loss-of-function in excitatory neurons [65].

SCN8A

The *SCN8A* gene encodes the pore-forming voltage-gated sodium channel subunit $Na_V1.6$, 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.

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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 comorbidi-

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

Gene	Clinical presentations	Medications
ALDH7A1	Neonatal onset drug resistant seizures which respond dramatically to pyridoxine Developmental delay/intellectual disability irrespective of pyridoxine supplementation	Pyridoxine, with arginine supplementation and/or lysine restricted diet [9].
CDKL5	Early infantile epilepsy (<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)	No available medication reported to show significant beneficial effects.
KCNQ2	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 Early infantile epileptic encephalopathy with drug resistant seizures as early as within first days of life, intellectual disability, and encephalopathic EEG	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].
KCNT1	EIMFS ADNFLE	Quinidine was not effective in ADNFLE patients [49]. Quinidine showed limited efficacy in EIMFS patients (responder rate=32%, n=25) [39,48,50-60].
SCN2A	Infantile epileptic encephalopathy with drug-resistant infantile-onset seizures (<12 months) and developmental delay Benign (familial) infantile seizures with infantile-onset seizures (<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 (>12 months)	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].
SCN8A	Drug resistant epilepsy with seizure onset age of <18 months and multiple seizure types including focal seizures, generalized seizures, and epileptic spasms, developmental delay/intellectual disability, and pyramidal and extrapyramidal symptoms	Sodium channel blockers are recommended, but supratherapeutic doses can be needed [77]. Levetiracetam can worsen the seizures [77].
STXBP1	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	Levetiracetam, vigabatrin, and valproic acid have been reported to be beneficial in small number of case reports [81,82,87-91].
SYNGAP1	Generalized epilepsy with eyelid myoclonia with absences and myoclonic-atonic seizures that are drug resistant, seizures triggered by eating, and developmental delay/intellectual disability	Valproate and lamotrigine are most frequently used [98].

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; *KCNT1*, 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 was reported.

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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-

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cilitated 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-

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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) 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 agreements, 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-

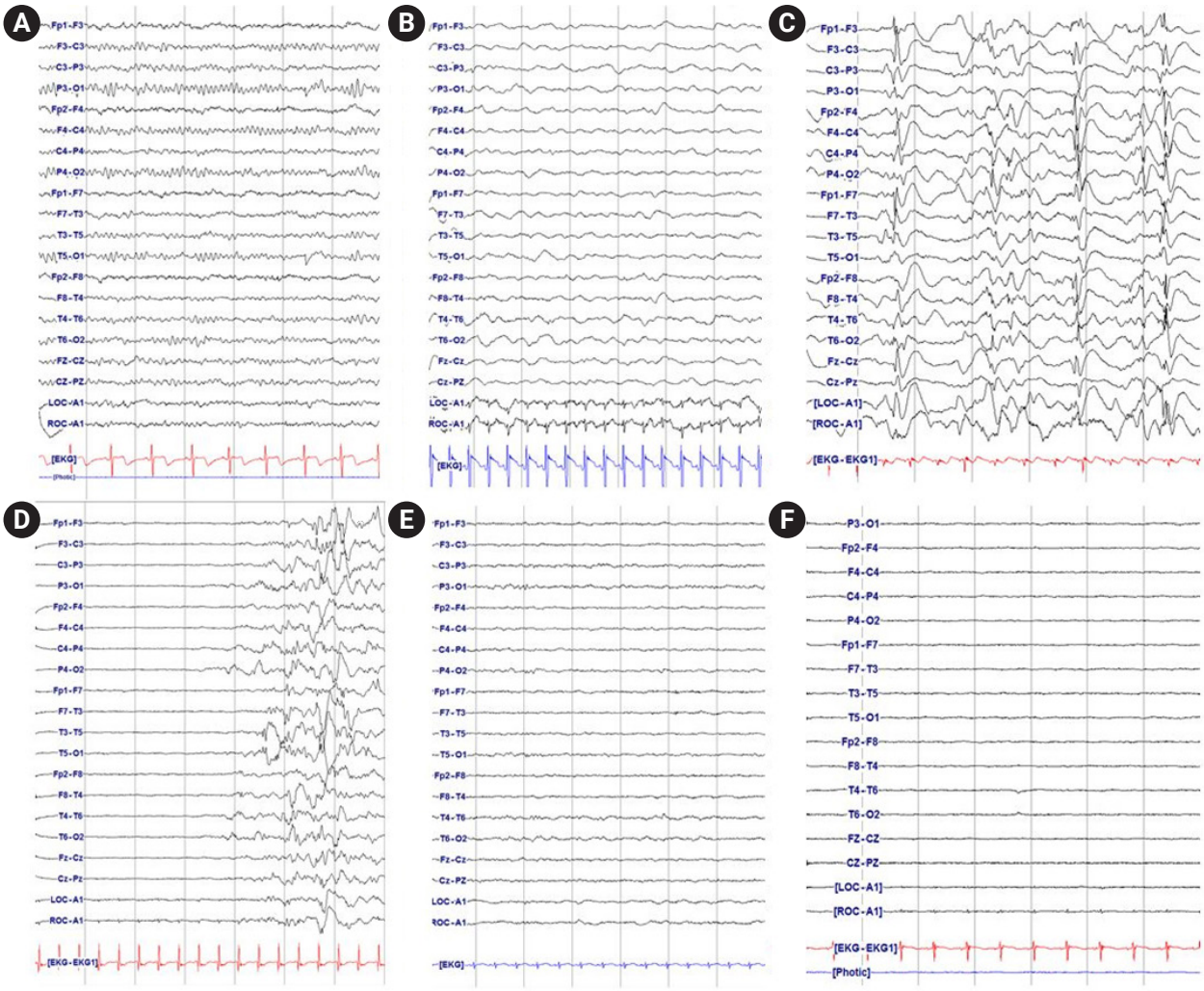

Fig. 1. Examples of background electroencephalography (EEG) rhythms of patients in the pediatric intensive care unit. (A) normal background EEG rhythm; (B) diffuse slowing background EEG rhythm (continuous EEG pattern with a dominant frequency less than that appropriate for age); (C) epileptiform (seizures and generalized periodic discharges); (D) burst-suppression (clear increases in amplitude of ≥20 μV, followed by inter-burst intervals of at least 1 second with low-voltage activity); (E) low-voltage (EEG activity of <20 μV); (F) isoelectric (without any visible EEG activity).

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

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

Characteristic	Total (n=113)	In-hospital mortality		
		Yes (n=43)	No (n=70)	*P* value
Age (yr)	2.0 (0.5–6.2)	4.8 (1.3–9.0)	1.2 (0.5–5.1)	0.012[a]
Male sex	65 (57.5)	24 (55.8)	41 (58.6)	0.773
IOD (day)	14 (7–32)	24 (10–55)	10 (6–22)	0.001[a]
HOD (day)	42 (22–86)	30 (15–58)	56 (25–93)	0.037[a]
Etiologies for PICU admission				0.744
HIE	35 (31.0)	14 (32.6)	21 (30.0)	
Non-HIE structural brain disease	31 (27.4)	11 (25.6)	20 (28.6)	
Non-structural brain dysfunction	41 (36.3)	17 (39.5)	24 (34.3)	
Others	6 (5.3)	1 (2.3)	5 (7.1)	
Reason for undergoing EEG				0.140
After anoxia/hypoxia	40 (35.4)	17 (39.5)	23 (32.9)	
Alteration in mental status	36 (31.9)	17 (39.5)	19 (27.1)	
Presence of seizures	20 (17.7)	6 (14.0)	14 (20.0)	
Suspicious movements	15 (13.3)	2 (4.7)	13 (18.6)	
Focal neurologic signs	2 (1.8)	1 (2.3)	1 (1.4)	
PRISM III-24	9 (3–14)	12 (7–16)	7 (2–12)	<0.001[a]
Time from PICU admission to EEG (hr)	19 (8–36)	19 (11–40)	18 (7–28)	0.191
EEG recording duration				0.843
Standard 30 min	93 (82.3)	35 (81.4)	58 (82.9)	
Continuous monitoring	20 (17.7)	8 (18.6)	12 (17.1)	
EEG background score	2 (2–5)	5 (3–6)	2 (2–3)	<0.001[a]
Absence of EEG reactivity	62 (54.9)	40 (93.0)	22 (31.4)	<0.001[a]
In-hospital mortality (yes)	43 (38.1)			
Sedation (yes)	37 (32.7)	18 (41.9)	19 (27.1)	0.106

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.
[a]Statistically significant clinical characteristics of critically ill patients according to in-hospital mortality.

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.

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

Table 2. Univariate analysis for mortality in sedated versus non-sedated groupsa

Variable	Sedated at the time of EEG recording (n=37)			Not sedated at the time of EEG recording (n=76)		
	In-hospital mortality (n=18)	Discharged (n=19)	*P* value	In-hospital mortality (n=25)	Discharged (n=51)	*P* value
Age (yr)	5.3 (0.8–9.9)	1.6 (0.5–6.6)	0.049[a]	2.4 (1.4–7.9)	1.1 (0.5–5.1)	0.191
Male sex	9 (50.0)	11 (57.9)	0.630	15 (60.0)	30 (58.8)	0.922
IOD (day)	31.5 (14.25–61)	15 (8–38)	0.130	19 (8–40)	10 (5–18)	0.024[a]
HOD (day)	47.5 (31.25–77.5)	68 (28.5–119)	0.451	20 (14–42)	47 (25–85)	0.295
Time from PICU admission to EEG (hr)	27 (19–41)	15 (5–21)	0.027[a]	15 (6–41)	19 (8–46)	0.671
EEG background score[b]	5 (2–5)	4 (2–5)	0.980	5 (5–6)	2 (2–2)	<0.001[a]
Absence of EEG reactivity	17 (94.4)	16 (84.2)	0.336	23 (92.0)	6 (11.8)	<0.001[a]
EEG duration (continuous)	4 (22.2)	3 (15.8)	0.619	4 (16.0)	9 (17.6)	0.858
PRISM III-24	13 (7–15)	9 (2–12)	0.037[a]	12 (7–17)	7 (2–12)	0.004[a]

Values are presented as median (interquartile range) or number (%).
EEG, electroencephalogram; IOD, duration of PICU admission; HOD, duration of hospital admission; PICU, pediatric intensive care unit; PRISM III-24, score of the pediatric risk of mortality III measured at the first 24 hours of PICU stay.
[a]Statistically significant clinical characteristics of sedated and non-sedated patients according to in-hospital mortality in univariate analysis; [b]Compared to EEG background score 1–2 (normal to diffuse slowing).

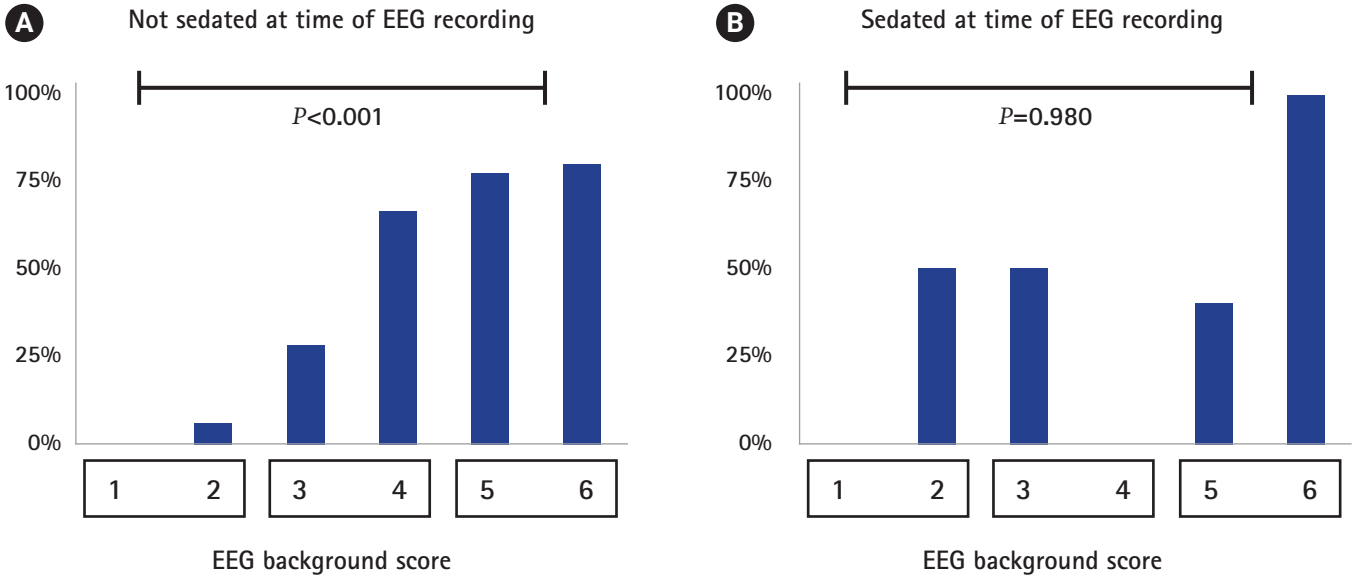

Fig. 2. Mortality rate of patients according to sedation at the time of electroencephalography (EEG) recording. (A) Not sedated at time of EEG recording. (B) Sedated at time of EEG recording.

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.

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Table 3. Adjusted analysis of the association between mortality and EEG (background score and reactivity) in non-sedated patients at the time of EEG recording

Variable	OR	95% CI	*P* value
EEG background score[a]			0.015[b]
Score 3 and 4	193.3	3.4–10,886.1	0.010[b]
Score 5 and 6	692.6	7.6–62,708.2	0.004[b]
Absence of EEG reactivity	234.1	9.4–5,831.9	0.001[b]

Adjusted for age at EEG recording, sex, IOD, HOD, lead time between PICU admission and EEG recording, duration of EEG recording, PRISM III-24.
EEG, electroencephalography; OR, odds ratio; CI, confidence interval; IOD, duration of PICU admission; HOD, duration of hospital admission; PICU, pediatric intensive care unit; PRISM III-24, score of the pediatric risk of mortality III measured at the first 24 hours of PICU stay.
[a]Compared with the EEG background score 1-2 (normal to diffuse slowing); [b]Statistically significant clinical characteristics of non-sedated patients according to in-hospital mortality in multivariable regression model.

Discussion

The relationship between EEG background rhythms and clinical outcomes has been demonstrated in previous studies, more frequently with cohorts of post-anoxic comatose patients after cardiac arrest. Quasiperiodic generalized spikes on a suppressed background, burst-suppression patterns, low-voltage backgrounds, and isoelectric patterns were each shown to be associated with mortality and poor neurologic outcome in post-anoxic comatose adult patients after cardiac arrest [4,14-17]. In addition, in a study with sedated or comatose adults in ICU with various underlying diseases, a burst-suppression pattern was associated with increased mortality; in another study with septic adult ICU patients, diffuse slowing, burst-suppression, and an isoelectric pattern were associated with mortality [3,4,18,19]. In children aged older than a post-conceptual age of 44 weeks, the available data are scant, but several studies have shown similar results to those of adult studies: epileptiform backgrounds, burst-suppression patterns, low-voltage backgrounds, and isoelectric backgrounds were associated with mortality and poor neurological outcomes in patients with HIE after cardiac arrest [20-23]. In children receiving critical care for reasons other than HIE, low-voltage, and isoelectric backgrounds were associated with poor outcomes in children with non-traumatic coma, diffuse slowing, epileptiform, and suppressed backgrounds were associated with mortality in children with acute liver failure, and diffuse slowing background was associated with poor outcomes in near-drowning encephalopathy patients [24-27].

Previous studies largely show the association between the absence of reactivity and increased mortality and morbidity in adult patients [3,4,19,21,28,29]. Although fewer studies were conducted 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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The Risk Factors and Clinical Features of Posttraumatic Seizure in Preschool-Aged Children

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Purpose: This study aimed to identify the clinical characteristics and risk factors of post-traumatic seizure (PTS) in preschool-aged children.
Methods: This study is based on a retrospective electronic medical record review of 1,576 children under 6 years old, who visited our hospital by head trauma from January 1, 2011 to December 31, 2015. We reviewed demographics, causes of head trauma, radiologic findings, Glasgow Coma Scale (GCS) score, and characteristics of seizure. PTS was divided into 3 groups of immediate (within the day of head trauma), early (within 7days) and late (after 7days) seizures.
Results: Of the 1,576 head traumas, 3.4% developed PTS of which 32.1% occurred immediately, 11.3% early, 56.6% lately. The mean age was 2.02±1.63 years and 60.6% was male, 2.6% had fever at the time of visit, and 2.9% had a history of seizures. The causes of head injuries were blunt trauma (34.5%), fall down (29.5%), slip down injury (25.1%), passenger traffic accidents (7.2%), pedestrian traffic accident (1.9%), and causes unknown (1.8%). The severity of traumatic brain injury (TBI) was mild in 99.0%, moderate in 0.4%, and severe in 0.5%. On radiologic findings, 88.6% was normal, 6.0% had skull fracture, 2.8% had intracranial hemorrhage (ICH) and 2.7% had both skull fracture and ICH.
Conclusion: The incidence of PTS in preschool-aged children was 3.4%. The risk factors for PTS in preschool-aged children were fever over 38.0˚C, history of seizure, TBI severity by GCS score. Age, sex, causes of head trauma, and radiologic findings did not correlated to the occurrence of PTS.

Keywords: Craniocerebral trauma; Brain injuries, traumatic; Seizures; Pediatrics

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

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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. Statistic 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℃. 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

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

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

Characteristic	Total	Immediate	Early	Late	*P* value
Total	53 (100.0)	17 (32.1)	6 (11.3)	30 (56.6)	<0.001
Interval (from head trauma to seizure occurrence) (day)					<0.001
Mean±SD	214.9±436.8	0±0	3.0±1.3	449.8±514.6	
Median (range)	18 (0–2,038)	0 (0–0)	2.5 (2–5)	197 (10–2,038)	
Character of seizure					0.235
Generalized convulsive	20 (37.7)	4 (20.0)	3 (15.0)	13 (65.0)	
Focal	33 (62.3)	14 (42.4)	3 (9.1)	16 (48.5)	
Duration of seizure (sec)					0.796
Mean±SD	250.94±365.79	185.0±162.5	570.8±927.0	215.4±186.5	
Median (range)	180 (5–2,400)	150 (20–600)	195 (5–2,400)	180 (10–600)	

Values are presented as number (%) unless otherwise indicated.
SD, standard deviation.

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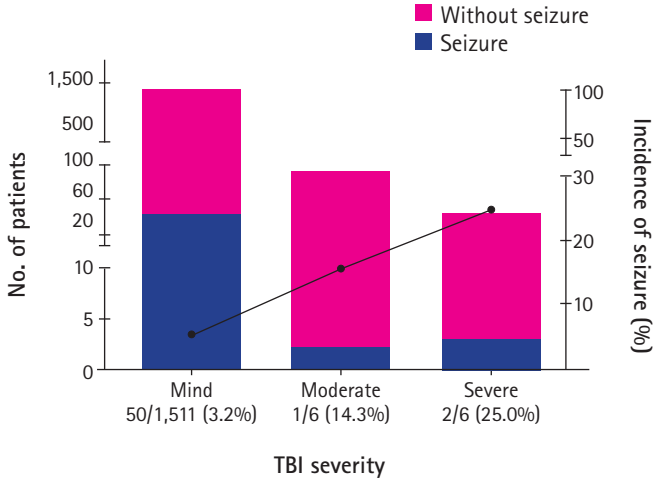

Fig. 1. Seizure incidence by traumatic brain injury (TBI) severity.

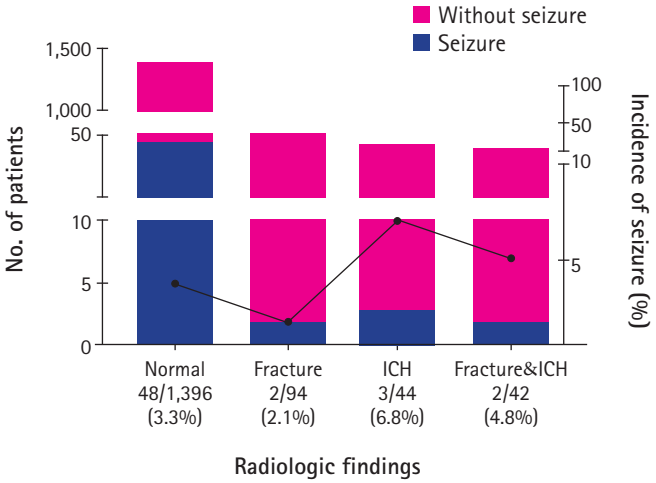

Fig. 2. Seizure incidence by radiologic findings. ICH, intracranial hemorrhage.

(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).

Discussion

It is known that PTSs occur in 5% to 10% of children, and the incidence recently reported in Korea was 12.3%, among which early seizure was 70.7% and late seizure was 29.3% [19]. It has been reported 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 children, among them, 43.4% of early seizures and 56.6% of late seizures occurred and 73.9% of early seizures showed immediate seizures. In previous studies, the study group was set up as an inpatient 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 population. 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 difference in inclusion criteria. In this study, patients with seizure with fever, with previous history of seizure attack, with a history of epilepsy were all included while most of previous studies excluded them. 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 epilepticus were observed 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 immediate PTS patients, 50.0% in early PTS, and 44.8% in late PTS. It is known that in posttraumatic epilepsy patients, the seizure usually occurs in the mesial temporal lobe or frontal lobe, and not frequently 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 generalized seizures or partial seizure with secondary generalization [24-28]. In this study, the incidence of generalized or partial seizures was analyzed but it was not analyzed for more detailed appearance of seizures, presence of secondary generalization, the relationship 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 except 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

in preschool-aged children, under 6 years. In this study, the risk factors for PTS were fever over 38.0℃ 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 prechool-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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Letter to the editor

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Idiopathic Median Mononeuropathy in a Previously Healthy Child: The Usefulness of Magnetic Resonance Imaging in Making the Diagnosis

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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

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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-

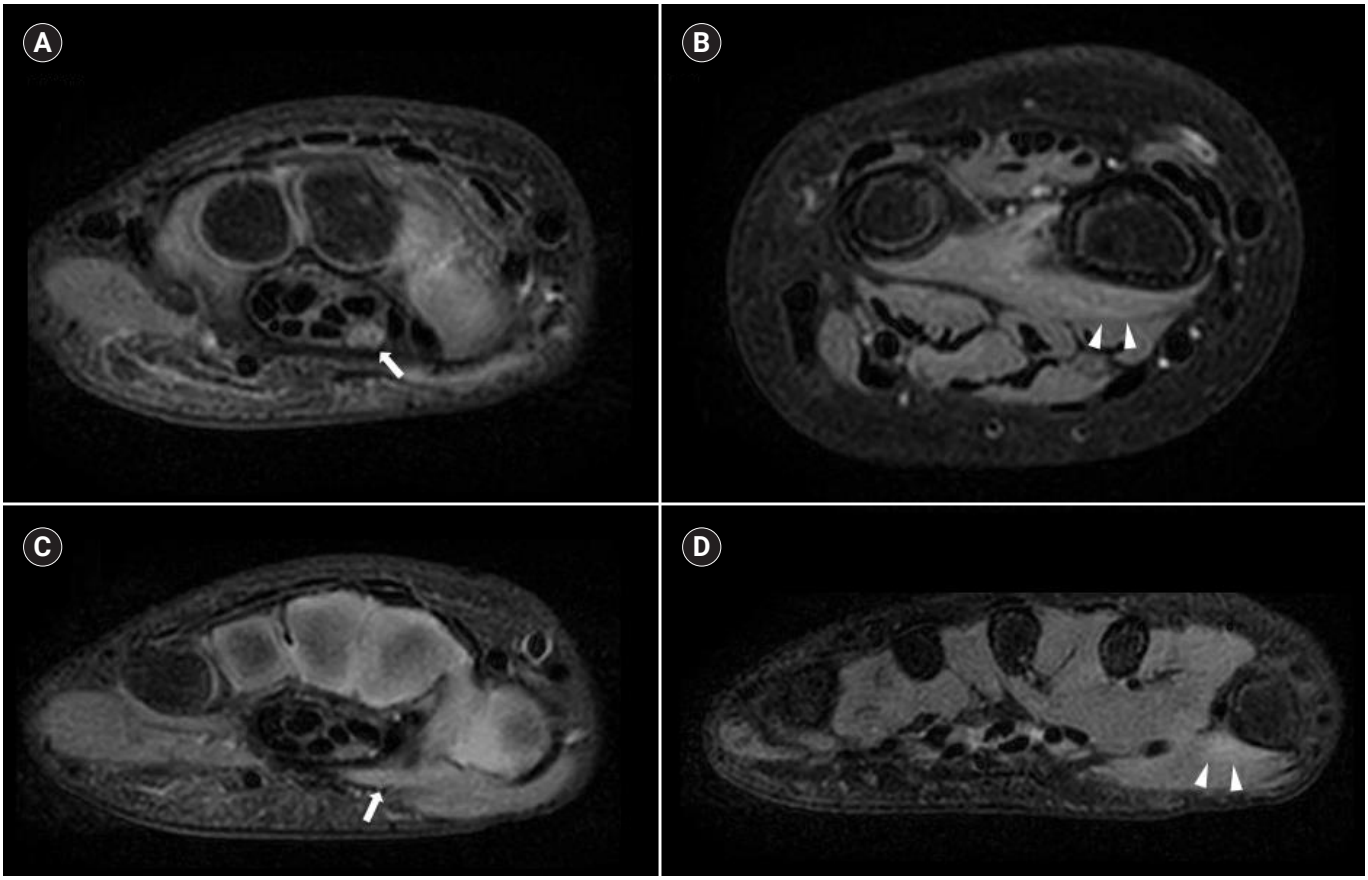

Fig. 1. Magnetic resonance imaging T2 fat saturated sequence with contrast enhancement of left wrist showing (A) swelling of the distal median nerve (arrow) and (B) increased T2 signal intensity in the pronator quadratus (arrowheads), and (C, D) abnormal T2 hyperintensity without definite atrophic changes on thenar muscles (arrow and arrowheads).

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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 was reported.

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Instructions to authors

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Manuscript preparation

1. General principles

1) *Annals of Child Neurology* publishes original articles, reviews, letters to the editor, and editorials.
2) The manuscript should not have been published previously, and not have been submitted for publication elsewhere. Any conflicts of interest of all listed authors should be stated.
3) The manuscript should be written according to the prescribed format. If not, the editorial board may return it before reviewing. The editorial board decides on publication and may modify a portion of the text with little effect on the original.
4) The manuscript must be written in English. Authors (particularly non-native English speakers) who submit the original article or letters to editor should check their manuscript by using professional editing service and submit the manuscript with a certificate of English review, including the name, institution, position, statement of approval, and signature with unstructured format.
5) The text of the manuscript, including tables and their footnotes and figure legends, must be double-spaced and in standard 12-point font on A4 paper size with left and right margin spaces of 2 cm and top and bottom margins of 3 cm.
6) Except for units of measurement, abbreviations are strongly discouraged. Do not use abbreviations in the title or abstract and limit their use in the text. Expand all abbreviations at first mention in the text.
7) Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) and laboratory values should be displayed in International System of Units (SI).
8) The number of pages of manuscripts of reviews and original articles has no limitation but no more than 10 printed pages are recommended. Letters to editor should be written in a maximum of 2 printed pages.

2. Cover letter

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

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

3. Original articles

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

Title page

The tile 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).

Introduction

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

Materials and Methods

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

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

Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.

Results

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

Discussion

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

Acknowledgment

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

ORCID

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

References

Reference citations in the text should be made with consecutive numbers in parenthesis (Vancouver style). References should be listed in the order of citation in the text, with the corresponding number. The reference style for journal articles is as follows : names of authors, full title of article, journal name abbreviated in accordance with MEDLINE, year, volume, and page numbers. List all authors when they are six or less; when they are seven or more, list the first six and add 'et al.'. The names of all authors must be listed by the last name and the initials of the first and middle names. Papers in press may be listed with the journal name and tentative year of publication. The style for a chapter of a book is as follows: author and title of the chapter, editor of the book, title of the book, edition, volume, place, publisher, year, and page

numbers. Cite unpublished data or personal communications in the text only and not in the reference list. Internet URLs should be as follows; authors' names, website title, URL and the time of the latest update. All other references should be listed as shown in the Recommendations from ICMJE. Authors are responsible for the accuracy and completeness of their references. The maximum number of cited references should be 40 for original articles and 5 for letters to editor.

Examples of reference styles

1) Journal article

1. Yoon JY, Kang MJ, Kim SY, Seo JY, Yang SW, Lee YA, et al. The relationship between initial body mass index and body mass index after one year of gonadotropinreleasing hormone agonist therapy in idiopathic true precocious puberty girls. J Korean Soc Pediatr Endocrinol 2011;16:165-71.
2. Wheless JW, Treiman DM. The role of the newer antiepileptic drugs in the treatment of generalized convulsive status epilepticus. Epilepsia 2008;49 Suppl 9:74-8
3. Gardos G, Cole JO, Haskell D, Marby D, Paine SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.
4. Nikitovic M, Wodchis WP, Krahn MD, Cadarette SM. Direct health-care costs attributed to hip fractures among seniors: a matched cohort study. Osteoporos Int In press 2012.

2) Book

- Book

5. Volpe JJ. Neurology of the newborn. 2nd ed. Philadelphia, PA: WB Saunders Co.; 1987.

- Book chapter

6. Pan ES, Cole FS, Weinttrub PS. Viral infections of the fetus and newborn. In: Taeusch HW, Ballard RA, Gleason CA, editors. Avery's diseases of the newborn. 8th ed. Philadelphia: Elsevier Saunders; 2005. p. 495-529.

- Abstract book or conference proceedings

7. Vivian VL. editor. Child abuse and neglect: a medical community response. Proceedings of the First AMA National Conference on Child Abuse and Neglect; 1984 Mar 30-31; Chicago. Chicago: American Medical Association; 1985.

- Thesis

8. Youssef NM. School adjustment of children with congenital heart disease (dissertation). Pittsburgh, PA: Univ. of Pittsburgh; 1988.

3) Website

9. On Ministry for Health, Welfare and Family Affairs. The Third Korea National Health and Nutrition Examination Survey (KNHANES III) [Internet]. Seoul: Ministry for Health, Welfare and Family Affairs; 2006 [cited 2006 Jul 8]. Available from: http://knhanes.cdc.go.kr.

Tables

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

Figures and figure legends

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

legend with complete sentences rather than incomplete phrases or a clause.

5) All symbols and abbreviations should be described below the figure.

4. Other types of manuscripts

All other types of manuscripts should meet the above mentioned requirements.

1) Reviews articles

Reviews may be written by invitation by the editorial board and provide concise reviews of important subjects to medical researchers. are organized as follows: title page, abstract and keywords, introduction, main text, conclusion, acknowledgments, references, tables, figure legends, and figures. An abstract is required but it need not be structured.

Reviews should not exceed 7,000 words, include no more than 6 figures or tables and 150 references.

2) Letters to the editor

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

3) Editorial

Editorials are invited by the editors and should be commentaries on articles published recently in the journal. Editorial topics could include active areas of research, fresh insights, and debates in all fields of child nerology. Editorials should not exceed 1,000 words, excluding references, tables, and figures, and no more than 2 figures or tables and 10 references.

Manuscripts accepted for publication

1. Final version

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

2. Manuscript corrections

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

3. Gallery proof

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

4. Feedback after publication

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

5. How the journal handle complaints and appeals

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

Who complains or makes an appeal?

Submitters, authors, reviewers, and readers may register complaints and appeals in a variety of cases as follows: falsification, fabrication, plagiarism, duplicate publication, authorship dispute, conflict of interest, ethical treatment of animals, informed consent, bias or unfair/inappropriate competitive acts, copyright, stolen data,

defamation, and legal problem. If any individuals or institutions want to inform the cases, they can send a letter via the contact page on our website: http://annchlidneurol.org. For the complaints or appeals, concrete data with answers to all factual questions (who, when, where, what, how, why) should be provided.

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

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

6. Page charge

There are no page charges to authors. All color figures and tables will be reproduced in full color in the online edition of *Annals of Child Neurology* at no cost to authors, but the complete cost in the printed version of the journal will be charged to the authors. Please contact the Editorial Office if you have any questions about potential fees.

7. Confirmation of acceptance

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

8. E-publication ahead of print

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

Further information

Any correspondence, queries or additional requests for information on the manuscript submission process should be sent to *Annals of Child Neurology* editorial office as follows:

Editor-in-Chief: Soonhak Kwon, MD
E-mail: editor@annchilneurol.org
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Name	Signature	Date

Author's checklist

1. General provisions

☐ The authors should ensure that the contents of the present manuscript have not been published nor intended to be published in other journals.

☐ The manuscript should be formatted as follows: A4 paper, 12 point font, left-aligned, double-spaced.

☐ An original article should be presented in the following order: cover page, abstract, keywords, introduction, methods, results, discussion, references, and captions and legends for tables and figures.

2. Cover page

☐ This section should indicate the contact information of the corresponding author: postal code, address, phone number, fax number, and email address.

☐ A running title should be given in 10 words or less.

3. Abstract and Keywords

☐ The abstract should be divided into Background and Purpose, Methods, Results, and Conclusions; it should be written in one paragraph that is within 250 words.

☐ Three to six keywords should be included (preferably those recommended in MeSH of Index Medicus; the first letter of each key word should be capitalized).

4. Main text

☐ The title should not include abbreviations; all the words must be spelled out.

☐ Information regarding approval of an institutional review board and obtaining informed consent should be mentioned in the Method section.

☐ References should be numbered in Arabic numbers in the order they are cited.

☐ Superscript numbers should come after commas and periods according to submission rules.

☐ When using abbreviations, their full forms should be used at first mention; abbreviations/acronyms should then be used consistently in further occurrences.

☐ Units of measure should be written in accordance with submission rules (except for % and °C, a space should come between the number and the unit of measure).

☐ For numbers, a comma should be inserted after every third digit.

☐ 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.