Aims and scope

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

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- Clinical neurophysiology
- Epilepsy
- Headache medicine
- Neuropsychiatric, neuromuscular medicine, neuroimmunology and inflammation
- Neuro-oncology
- Sleep medicine
- Vascular neurology
- Other diseases affecting the developing nervous system.

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Dear Member of the Editorial Board,

Thank you for allowing me to take this opportunity to congratulate you all on the decision of the Content Selection and Advisory Board of SCOPUS to include Annals of Child Neurology into SCOPUS. This is a wonderful achievement and it reflects positively on the hard work and daring initiative of the board. This success was also achieved in a remarkably short period of time. In many ways, it parallels the larger extraordinary academic achievements of child neurology in South Korea. In my opinion, based on years of association with many Korean child neurologists and first hand experience gleaned by attending your professional meetings, this decision underscores the fact that child neurology in South Korea is second to none. Even though child neurology is a relatively new specialty within South Korea the world has already benefited from the many professional contributions that have been accepted into the most prestigious academic neurological journals. Now, Annals of Child Neurology has passed another milestone of international professional recognition which will allow even more contributions to be shared with the greater child neurology community. The pace of progress is very impressive. Godspeed.

Sincerely,

Douglas R. Nordli Jr, MD

Conflicts of interest

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

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Introduction

Movement disorders often arise from the basal ganglia nuclei or when their connections malfunction, resulting in hypokinetic, hyperkinetic, or dystonic disorders [1]. A seizure is the result of abnormally excessive or synchronous neuronal activity in the brain, defined as "momentary arising of signs and/or symptoms," whereas epilepsy is characterized by one or more seizures with a relatively high recurrence risk [2]. Although they are caused by a number of different conditions, both movement disorders and seizures present abnormal movements with coinciding phenomenology [3]. Both movement disorders and epilepsy occur in many genetic disorders ranging from inborn errors of metabolism to developmental and epileptic encephalopathies, epilepsy syndrome with stereotypies, and paroxysmal dyskinesias [3,4].

Paroxysmal dyskinesias are an important disease paradigm associated with overlapping movement disorders and seizures [5]. In many paroxysmal dyskinesias, movement disorders and seizures occur simultaneously at the time of, before, or even a long time after diagnosis. The most well-known is paroxysmal kinesigenic dyskinesia (PKD) in which PRRT2 mutations have been identified. In this case, infantile convulsions often occur in advance [6]. With the development of exome sequencing in recent years, many genetic abnormalities identified in epilepsy that occur in conjunction with paroxysmal dyskinesias have been identified [3,7-9]. This review aims to gather the most updated literature regarding paroxysmal movement disorders, and seizures and we will discuss the genetic abnormalities that come with seizures for each paroxysmal
movement disorders. Table 1 summarizes the clinical manifestations of each epilepsy-paroxysmal movement disorders.

## Clinical overview

Paroxysmal dyskinesias have distinct features with episodic occurrences of involuntary extrapyramidal movements [3]. It is a heterogeneous disorder group characterized by episodes of abnormal involuntary movements, such as chorea, dystonia, and ballism [3]. Most of these movements do not cause loss of consciousness but sometimes a sensory aura precedes them [3]. Some clinicians may mistake these movements for focal seizures, either focal aware seizure or focal impaired awareness seizure [3]. In such cases, the absence of ictal discharges in a scalp electroencephalography may be helpful in the diagnosis of paroxysmal dyskinesias [2].

Paroxysmal dyskinesias are divided into three clinical syndromes (Fig. 1): PKD, paroxysmal non-kinesigenic dyskinesia (PNKD), and paroxysmal exercise-induced dyskinesia (PED) [6,8]. PKD is the most common type and is caused by voluntary movements, such as standing from a seated position or transitioning from walking to running. PKD attacks usually develop during childhood and are well controlled by carbamazepine [5,10]. Infantile convulsions, often with choreoathetosis, frequently precede PKD [6]. PNKD attacks are usually triggered by alcohol, coffee, or strong emotions [6], and can often last longer than PKD attacks ranging from 10 minutes to an hour and even up to 12 hours [6]. However, their frequency is low, typically occurring only a few times a year [6]. Of the three paroxysmal movement disorders, PED is the rarest. PED attacks are induced by physical exertion after long periods of exercise with migraines, hemiplegia, ataxia, and epilepsy being associated with PED [6,11].

In terms of co-occurrence with epilepsy, patients with mutations in PRRT2 [9,12], SCN8A [13,14], SLC16A2 [15,16], and CHRNA4 [17] have been reported in PKD (Fig. 1). In PNKD, CACNA1A [18] and KCNMA1 [19]-related diseases have been reported, while SLC2A1-related glucose transporter-1 (GLUT1) protein deficiency [6] and recently, TBC1D24 mutations, have been reported in PED [20]. Other paroxysmal movement disorders associated with epilepsy include hemiplegic migraine and episodic ataxias. A combination of familial hemiplegic migraine and epilepsy have been found in PRRT2, CACNA1A, SCN1A, and ATP1A2 mutation-positive patients [8,21]. In addition, PRRT2 [8], CACNA1A [18], and KCNMA1 [8,22,23] mutations are mainly responsible for the co-occurrence of episodic ataxias and epileptic seizures.

### Table 1. Summary of clinical manifestations of epilepsy-paroxysmal movement disorders

<table>
<thead>
<tr>
<th>Pathomechanism</th>
<th>Gene</th>
<th>Characteristics of the genes and encoded proteins</th>
<th>Inheritance</th>
<th>Paroxysmal MDs</th>
<th>Associated disorder and seizure types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Channelopathy</td>
<td>SCN8A</td>
<td>Sodium voltage-gated channel a subunit 1</td>
<td>AD</td>
<td>PKD</td>
<td>BFIS, ICCA, GTCS, DEE</td>
</tr>
<tr>
<td></td>
<td>SLC16A2</td>
<td>Encodes monocarboxylate transporter 8</td>
<td>X-linked</td>
<td>PKD</td>
<td>Allan-Herndon-Dudley syndrome, Febrile, myoclonic, GTCS</td>
</tr>
<tr>
<td></td>
<td>CHRNA4</td>
<td>Encodes neuronal nicotinic acetylcholine receptor a4 subunit</td>
<td>AD</td>
<td>PKD</td>
<td>Febrile, GEFS+, myoclonic, GTCS</td>
</tr>
<tr>
<td>Synaptopathy</td>
<td>PRRT2</td>
<td>Proline-rich transmembrane protein 2</td>
<td>AD</td>
<td>PKD, HM, EA</td>
<td>BFIS, ICCA, absence, febrile, paroxysmal dystonia</td>
</tr>
<tr>
<td>Synaptopathy</td>
<td>CACNA1A</td>
<td>Calcium voltage-gated P/Q type channel a subunit 1</td>
<td>AD</td>
<td>PNKD, HM, EA</td>
<td>Spinocerebellar ataxia type 6, IS, DEG, febrile, GEFS+, absence, generalized, focal, status epilepticus</td>
</tr>
<tr>
<td>Synaptopathy</td>
<td>KCNMA1</td>
<td>Potassium calcium-activated channel subfamily M a1</td>
<td>AD</td>
<td>PNKD</td>
<td>Absence, GTCS, clonic, atonic</td>
</tr>
<tr>
<td>Transportopathy</td>
<td>SLC2A1</td>
<td>Solute carrier family 2 member 1 encoding glucose transporter type-1</td>
<td>AD</td>
<td>PED</td>
<td>GLUT1 deficiency, GTCS, absence, myoclonic, focal</td>
</tr>
<tr>
<td>Synaptopathy</td>
<td>TBC1D24</td>
<td>Encodes TBC protein which interacts with GTPases involved in the regulation of membrane trafficking</td>
<td>AR, AD</td>
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<td>IS, EIMFS, absence, clonic, febrile, focal, GTCS, myoclonic tonic</td>
</tr>
<tr>
<td>Transportopathy</td>
<td>ATP1A2</td>
<td>a2 subunit of Na+/K+ ATPase</td>
<td>AD</td>
<td>HM</td>
<td>BFIS, focal seizure, febrile</td>
</tr>
<tr>
<td>Channelopathy</td>
<td>SCV1A</td>
<td>a1 subunit of the sodium channel</td>
<td>AD</td>
<td>HM</td>
<td>Dravet syndrome, GEFS+, MAE, EIMFS</td>
</tr>
<tr>
<td>Channelopathy</td>
<td>KCNA1</td>
<td>Potassium voltage-gated channel</td>
<td>AD</td>
<td>EA</td>
<td>Tonic-clonic, focal, photo-sensitive</td>
</tr>
</tbody>
</table>

Causative genes are listed in order of the main type of movement disorders:
- MD, movement disorder; AD, autosomal dominant; PKD, paroxysmal kinesigenic dyskinesia; BFIS, benign familial infantile seizures; ICCA, infantile convulsion with choreoathetosis; GTCS, generalized tonic-clonic seizures; DEE, developmental epileptic encephalopathy; GEFS+, genetic epilepsy with febrile seizures plus; HM, hemiplegic migraine; EA, episodic ataxia; IS, infantile spasms; PNKD, paroxysmal non-kinesigenic dyskinesia; LGS, Lennox-Gastaut syndrome; PED, paroxysmal exercise-induced dyskinesia; GLUT1, glucose transporter-1; AR, autosomal recessive; EIMFS, epilepsy of infancy with migrating focal seizures; MAE, myoclonic-ataxic epilepsy.
Historically, paroxysmal dyskinesias and other episodic neurological disorders have been considered an ion channel dysfunction [5]. Accordingly, it has been suggested that the relationship between paroxysmal dyskinesias and epilepsy is in the form of "basal ganglia epilepsy," meaning that paroxysmal dyskinesias attacks are due to the altered functions of ion channels in both the cortex and subcortex [26]. However, with the discovery of the major paroxysmal dyskinesias genes PRRT2 and SLC2A1, the hypothesis of channelopathy lost its strength because neither encoded ion channels [5]. While novel mutations in genes related to ion channel function, such as KCNA1, KCNMA1, SCN8A, and CACNA1A, have recently been described, genes encoding synaptic proteins/receptors, such as PRRT2, CHRNA4 and transporters including, SLC2A1, SLC16A2, and ATP1A2, have also been identified (Fig. 1) [5]. As the understanding of the genetic basis of epilepsy syndrome and paroxysmal dyskinesias increase, it provides insights into the shared mechanisms behind the two conditions and reveals the role of ion channels and the proteins associated with vesical synapse or energy metabolism [5,6,14,27].

**PKD and epilepsy**

1. **PRRT2**

PRRT2, which represents proline-rich transmembrane protein 2, encodes a transmembrane protein involved in synaptic transmission, although its function is relatively unknown [12]. Genetic mutations of PRRT2 not only occur in PKD patients, but also in most cases of benign infantile familial seizure, infantile convulsions with paroxysmal choreoathetosis (infantile convulsion with choreoathetosis), frequent cases of hemiplegic migraine, and in a minority of cases of episodic ataxias, childhood absence epilepsy, paroxysmal torticollis, and febrile seizure [5,8,12].

PKD affects about 1:150,000 in the general population [12]. As is well known, the major gene responsible for PKD is PRRT2, and according to the case ascertainment, the frequency ranges from about 40% to 90% or more [5,6,12,28]. A majority of PRRT2 cases have an obvious kinesigenic trigger with anxiety or prolonged exercise triggering PKD attacks in up to 40% of cases [5]. PKD attacks are typically very short (i.e., less than 1 minute), but with a high frequency (i.e., occurs more than once daily). They usually consist of chorea and dystonia but also rarely athetosis, ballism, hemiballism, tongue movements, perioral dyskinesias, and clawing of the hands or a frozen gaze [5,12]. The attacks are bilateral or some-
times unilateral and tend to generalize [5,12]. Symptoms most commonly manifest shortly before or during puberty in PRRT2 mutation carriers with less than 5% of PRRT2-associated cases experiencing an onset after 18 years of age [12]. Patients often experience several attacks a day but regardless of treatment, the frequency decreases with advancing age after puberty [5].

Benign infantile familial seizure is inherited in an autosomal dominant pattern with up to 80% of cases exhibiting mutations in PRRT2 [3,12]. It is characterized by seizures that occur between 3 and 12 months of age [10] and involve brief, focal motor manifestations accompanied by cyanosis, hypertonia, and limb jerks [3,12]. They can occur in clusters of multiple seizures, up to eight to ten seizures per day, which occur every 2 to 3 hours on average [10]. However, patients have an excellent response to antiepileptic drugs and seizures generally resolve by the age of 2 years [12,29]. That aside, patients demonstrate normal developmental outcomes, neurological examinations, brain imaging patterns, and electroencephalography background signals [10].

Similarly, nearly 90% of infantile convulsion with choreoathetosis syndrome patients have PRRT2 mutations [5]. Overall, the clinical findings and genetic features overlap with cases of PKD and benign infantile familial seizure. This syndrome is characterized by the development of PKD after infantile convulsions (PKD usually develops by the age of 5 years) as some epileptic seizures may exhibit at a much later age than typical benign infantile familial seizure [5]. Remission rate for treated infantile convulsion with choreoathetosis cases is up to 89%, which means that only a small number of patients maintain partial response to therapy [12].

The PRRT2 gene has recently been implicated in the shared pathophysiology of epilepsy and hemiplegic migraine [30]. Although PRRT2 mutations are rare, they have also been identified in hemiplegic migraine with PKD, and/or benign infantile familial seizure [31]. Interestingly, CACNA1A, ATP1A2, or SCN1A genes, or in certain combinations, have been found in approximately 75% of familial hemiplegic migraine patients and also in a smaller number of sporadic hemiplegic migraine patients [32].

Historically, PKD, infantile convulsion with choreoathetosis, and benign infantile familial seizure have been considered to be allelic disorders because they occurred together in some families and were linked to the same region on chromosome 16p11.2-q12.1 [33,34]. In 2011, Chen et al. [9] first identified mutations of PRRT2 located on chromosome 16p11.2 in eight Chinese PKD families by whole exome sequencing. A significant number of PRRT2 mutations associated with loss-of-function and missense amino-acid change mutations have since been identified [6]. To date, a total of 97 different PRRT2 mutations have been reported [35], of which c.649dupC is a hotspot. It is found in 60% to 80% of PRRT2-associated PKD, benign infantile familial seizure, and infantile convulsion with choreoathetosis [12]. In addition, deletion mutation at the same location (c.649delC; approximately 4%) and at the more proximal part (c.291delC; approximately 2%) have also been identified [12]. However, a c.579dupA mutation of the PRRT2 gene presents more commonly in infantile convulsion with choreoathetosis [12].

The PRRT2 gene comprises of four exons that encodes the 340-amino acid, proline-rich transmembrane protein 2 [12]. PRRT2 is found throughout the central nervous system, especially at high expression levels in the cortical layers of the cerebral cortex, basal ganglia, and cerebellum [9]. The contribution of alteration of the basal ganglia-thalamocortical circuit to the pathogenesis of PRRT2-associated PKD has been proposed [36,37]. It is mainly recognized in the axons but not in the dendrites of neurons at the subcellular level [12]. A yeast two-hybrid assay found that PRRT2 interacts with the synaptic t-SNARE protein synaptosomal-Associated Protein, 25kDa (SNAP25) [38,39]. SNAP25 alters neurotransmitter release and calcium channel dynamics, which affects vesicle synaptic accordingly [40]. It has been suggested that PRRT2 mutations impair SNAP25 function by altering Cav2.1 activity, which lead to neuronal hyperexcitability and subsequently cause epilepsy, PKD, or other paroxysmal movement disorders [41]. In addition to the relation between PRRT2 and SNAP25, many studies proposed that PRRT2 has postsynaptic roles in alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor signaling [42,43].

In addition to the roles at the synapse, recent studies have suggested that PRRT2 interacts with ion channels, such as Nav1.2/Nav1.6 channels, major regulators of the excitability of excitatory neurons, but not with Nav1.1 channels, which is essential for the excitability of inhibitory neurons [44]. Thus, the disturbance in cellular excitability by lack of negative modulation of Na+ channel was assumed to be the main pathogenetic mechanism of paroxysmal character [44].

Currently, there is no clear evidence to propose genotype-phenotype correlations [12,35]. Variable phenotypes are found within and between families with the same PRRT2 mutations [10]. Patients with a 16p11.2 deletion not only have PRRT2-PKD but also additional clinical features, including developmental delay, intellectual disability, and/or autism spectrum disorder [45,46]. Analogously, patients with biallelic PRRT2 mutations often show more severe phenotypes, including intellectual disability, episodic ataxia, and different seizure types [47,48].

2. SCN8A
Pathogenic variants of SCN8A, which encode the sodium channel
voltage-gated α8-subunit (Nav1.6), have originally been described in patients with developmental and epileptic encephalopathies [13,49]. However, recent studies showed that SCN8A pathogenic variants have a wide phenotypic spectrum ranging from developmental and epileptic encephalopathies to behavioral disorders or movement disorders [50]. A variety of seizure types along with episodes of paroxysmal dystonia, sometimes resembling PKD, can be caused by mutations in SCN8A [5,14].

Clinical syndromes of PRRT2 mutations (PKD, benign infantile familial seizure, and infantile convulsion with choreoathetosis) have been reported in patients with SCN8A mutations [14]. Some individuals manifest either with afibrile focal or generalized tonic-clonic seizures during the first 2 years of life, often having paroxysmal dyskinetic/dystonic episodes in puberty, which can be triggered by movement initiation (e.g., stretching) and/or emotional stimuli [14]. Choreo-dystonia and dystonic dyskinesias present in some individuals with SCN8A-related epileptic encephalopathies [13], which suggests that episodic movement disorders also occur with pathogenic variants of SCN8A.

Patients with mutations in PRRT2 and SCN8A have similar clinical manifestations, but there are many significant findings that help differentiate the diagnosis [13]. SCN8A patients have a variety of seizure types along with focal, tonic, clonic, myoclonic, and absence seizures, and they are usually refractory to antiepileptic drugs [14]. Furthermore, regardless of whether early development was normal, patients with SCN8A mutations develop moderate to severe intellectual disability [13] and might coincide with non-epileptic paroxysmal movement disorders, including dystonia and ataxia [13]. In addition, most SCN8A mutations are de novo but only one case of somatic mosaicism in an unaffected parent has been reported [13]. All these characteristics make SCN8A-related disorders different to that of PRRT2.

3. SLC16A2
The SLC16A2 gene located on chromosome Xq13.2 encodes for monocarboxylate transporter 8 (MCT8), which is an active transporter protein in humans [16]. MCT8 transports diverse iodo-thyronines including triiodothyronine (T3) and thyroxine (T4) [16]. MCT8 deficiency, also known as Allan-Herndon-Dudley syndrome, is characterized by an increased level of free T3, normal to low free T4, low reverse T4, and normal to elevated thyroid stimulating hormone without any signs or symptoms of congenital hypothyroidism [15]. Clinical characteristics consist of variable mental retardation, hypotonia, spasticity and pyramidal signs, facial/neck weakness, ataxia, and paroxysmal purposeless movements with a static or slow progressive course [15,16].

Epileptic seizures, including febrile seizure, myoclonic seizure, and generalized tonic-clonic seizures, are found in almost half of Allan-Herndon-Dudley syndrome [16,51,52]. Involuntary movements, including dystonic and/or athetoid and characteristic paroxysms or kinesigenic dyskinesias, are common in affected males [15,53]. Attacks manifest through stretching of the body, opening of the mouth, or extending or flexing of the limbs for 1 to 2 minutes [53]. Somatosensory stimuli, including the changing of clothes or diapers, or lifting the affected child can trigger attacks [53].

Although the MCT8 defect has previously been noted in patients with thyroid abnormalities [54,55], the cause behind the abnormal paroxysmal involuntary movements are still unclear [15].

4. CHRNA4
CHRNA4, which encodes the α4 subunit of the neuronal nicotinic acetylcholine receptor (nAChR), frequently assembles with the β2 subunit (encoded by CHRN2) to form a heteropentamer α4β2-nAChR [56]. Pathogenic variants of CHRNA4 have been found to be the major cause of autosomal dominant nocturnal frontal lobe epilepsy, which causes frequent motor seizures during non-rapid eye movement sleep [57].

Recently, Jiang et al. [17] found that co-occurrence of genetic epilepsy with febrile seizures plus and PKD have CHRNA4 mutations in PRRT2-negative families. Different seizure types were observed, including recurrent febrile seizures, which occurred between the ages of 3 and 7 years, afibrile seizures, including myoclonic seizures, which occurred between the ages of 6 and 11 years, and generalized tonic-clonic seizures, which occurred after the age of 14 years [17]. Symptoms of choreoathetosis and dystonia were mostly triggered by sudden movements and only occurred during daytime [17]. The attacks usually lasted for less than 30 seconds and did not cause any loss of consciousness and with oxcarbazepine monotherapy, they were markedly controlled [17].

PNKD and epilepsy

1. KCNMA1
The KCNMA1 gene encodes the α subunit of the large conductance, voltage, and calcium-sensitive potassium channel, which is also activated by the concentration of cytosolic Mg2+, and is known to be predominantly expressed in the amygdala, caudate nucleus, cerebral cortex, hippocampus, hypothalamus, spinal cord, and Purkinje cells in the cerebellum [58,59]. Heterozygous mutations in KCNMA1 were first reported in a large family with generalized epilepsy and PNKD [27]. Recently, homozygous KCNMA1 mutations was illustrated in patients with cerebellar atrophy, developmental delay, and seizures [60].
Mutations in the KCNMA1 gene produce a syndrome of PNKD and epilepsy, either in the form of absence seizures or generalized tonic-clonic seizures [5,19]. In 2005, Du et al. [27] reported a family with an autosomal dominant form of generalized epilepsy and paroxysmal dyskinesias carrying a mutation in the KCNMA1 gene. Clinically, paroxysmal dyskinesias attacks that involve KCNMA1 mutations were described to resemble the non-kinesigenic variant with alcohol being a possible trigger [27]. Recent studies established a correlation of the homozygous KCNMA1 mutation with cerebellar ataxia, cortico-cerebellar tract atrophy, developmental delay, paroxysmal dyskinesia, and variable epilepsies, including absence, myoclonic, atonic, tonic, and generalized tonic-clonic seizures [19,60]. In addition, both gain- and loss-of-function have been proposed as the underlying molecular mechanism behind the channelopathy, which causes an increase in excitability [60].

**PED and epilepsy**

1. **SLC2A1**

   GLUT1 deficiency syndrome is caused by mutations in SLC2A1, which presents early-onset refractory seizures, PED, and movement disorders [6]. SLC stands for solute carrier, while 2A1 represents the family number 2 and member number 1 in the family. As GLUT1 is one of the proteins located on the blood-brain barrier, GLUT1 deficiency syndrome was previously described in association with infantile epilepsy with low cerebrospinal fluid glucose [61]. Both epilepsies, particularly early-onset absence, and PED co-occur in families and individuals [5].

   This disorder is usually classified into two groups: classical and nonclassical. Classical or typical GLUT1 deficiency involves infantile-onset, pharmaco-resistant epilepsy, intellectual disability, microcephaly, and complex movement disorders; while nonclassical or atypical GLUT1 deficiency involves paroxysmal movement disorders, atypical childhood absence epilepsy, and myoclonic astatic epilepsy [61]. Infantile-onset epilepsy can be alleviated during childhood but movement disorders tend to emerge later, which may be due to changes in brain metabolism over time [62].

   Approximately 90% of patients have clinical seizures, mainly generalized tonic-clonic seizures followed by absence, myoclonic, and focal onset seizures [61]. The PED attacks usually consist of choreathetosis and dystonia, which mainly affect the lower limbs, and are typically triggered by sustained exercise [5]. Notably, this disturbance might be misdiagnosed as epileptic myoclonic seizures [63]. The combination of epilepsy with a possible family history and PED in the setting of an unremarkable neurological examination, along with low cerebrospinal fluid glucose concentration, represents an important clinical clue to raising the correct diagnostic suspicion [5]. An early diagnosis of GLUT1 deficiency is crucial given that the syndrome can be well managed with a ketogenic diet [5,61].

   Although isolated PED caused by SLC2A1 mutations are rare, episodes of PED in those suffering from GLUT1 deficiency syndrome are common but often go unnoticed in the setting of epilepsy or more severe findings [61]. Isolated dystonia after exercise that usually only affects the lower limbs have also been observed in carriers of SLC2A1 mutations that cause early-onset Parkinsonism or dopa-responsive dystonia; however, these are rather unusual initial presentations of these conditions [8].

   No clear-cut phenotype-genotype correlations have been established [64]. Patients exhibited interindividual phenotypic variability despite having the same mutations, which suggests the presence of genetic modifiers, such as secondary genes [61,64]. Therefore, the genotype does not always predict the phenotype [61].

2. **TBC1D24**

   The gene TBC1D24 is involved in the regulation of synaptic vesicle trafficking by interacting with GTPase in brain and somatic development [65,66]. Genetic mutations in TBC1D24 have been associated with multiple phenotypes with epilepsy as the main clinical manifestation [20,66]. Epilepsy aside, TBC1D24 is also associated with deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures (DOORS syndrome), as well as nonsyn-dromic deafness [65].

   The types of seizures and epilepsies are diverse. Seizure types include infantile spasms, febrile convulsions, myoclonic, clonic, tonic, absence, tonic-clonic seizures with or without apparent focal onset, and focal seizures with retained or impaired awareness [65]. Myoclonic or clonic seizures are the most frequent seizure types, which include infantile and progressive myoclonic epilepsies, as well as familial epilepsy of infancy with migrating focal seizures and are often unresponsive to medication [65].

   TBC1D24 epilepsy syndromes occur with both compound heterozygous and homozygous recessive mutations. More than 50 missense and loss-of-function mutations have been described and associated with the exercise-induced dystonia phenotype, which persist into adulthood according to a long clinical follow-up study [20]. The additional diversity of TBC1D24 phenotypes might be due to its broader expression patterns; TBC1D24 is expressed in several human tissues with the highest expression occurring in the brain in multiple cerebral areas, including all layers of the cerebral cortex and the hippocampus [66]. In a Drosophila model, some mutations of TBC1D24 cause activity-induced locomotion and synaptic vesicle trafficking defects, which is consistent with exacer-
bated oxidative stress sensitivity, suggesting that these mutations cause dysfunctional, sustained movement disorders [20].

Other paroxysmal movement disorders and epilepsy

1. Familial hemiplegic migraine and epilepsy

CACNA1A, ATP1A2, SCN1A, and PRRT2 genes often contain one or more mutations in both epilepsy and hemiplegic migraine patients [8,21,41]. These shared mutations identified in epilepsy and migraine cases suggest that there is a common genetic basis for these conditions. There are two categories of migraine: migraine with and without aura, and hemiplegic migraine is a rare form of migraine with aura [41].

1) ATP1A2

The ATP1A2 gene is located on chromosome 1q23 and encodes for the α2 subunit of Na+/K+ ATPase, which consists of an α and a β subunit. ATP1A2 mutations were identified in families with familial hemiplegic migraine, called familial hemiplegic migraine type 2 [67,68].

The incidence of epilepsy is increased in families with familial hemiplegic migraine type 2, where approximately 20% experience seizures, such as focal seizures, benign infantile familial seizure, and high fever convulsions [68]. In a family with familial hemiplegic migraine type 2, one member had focal epilepsy as a child and electroencephalography revealed a focal migratory epilepsy-like discharge waveform [68].

Since maintaining the correct concentrations of Na+ and K+ via the Na+/K+ ATPase system is crucial for the ability of astrocytes to clear extracellular glutamic acid, an abnormal Na+/K+ ATPase system function disrupts the K+ gradient and impairs glutamate clearance, which likely contributes to the development of familial hemiplegic migraine and epilepsy [41].

2) SCN1A

SCN1A, which encodes the a1 subunit of the sodium channel, is associated with a range of human diseases [69]. The most well-recognized epilepsy phenotype associated with SCN1A is the Dravet syndrome but it also results in several other epilepsy syndromes ranging from self-limited and pharmacoresponsive epilepsies, such as genetic epilepsy with febrile seizures plus, Dravet syndrome, myoclonic-ataxic epilepsy, and epilepsy of infancy with migrating focal seizures. SCN1A disorders also result in other neurological disorders such as hemiplegic migraine, intellectual disability, and autism spectrum disorder [69].

Familial hemiplegic migraine type 3 is caused by heterozygous pathogenic variants of the SCN1A [70]. In contrast to familial hemiplegic migraine due to CACNA1A and ATP1A2 mutations, in the few patients with familial hemiplegic migraine type 3 carrying SCN1A mutations and presenting with seizures [69], hemiplegic migraine attacks are always independent from seizures and the two phenotypes do not generally overlap temporally [69].

All SCN1A mutations reported in familial hemiplegic migraine type 3 are missense mutations. Most experimental results show that they cause a gain-of-function of Nav1.1 [71]. Cellular and animal data point to an increased excitability of gamma-aminobutyric acid (GABAergic) neurons in familial hemiplegic migraine type 3, which is a different mechanism from that seen in epileptogenic Nav1.1 mutations [69].

Episodic ataxia and epilepsy

Episodic ataxia is a rare neurological condition characterized by recurrent spells of truncal ataxia and incoordination. PRRT2, CACNA1A, and KCN1 mutations are mainly responsible for co-occurrence of episodic ataxias and epileptic seizures [24,25].

1) CACNA1A

CACNA1A is located on chromosome 19p13 and encodes for the a1 subunit of the Cav2.1 P/Q-type voltage-gated calcium channel [18]. Pathogenic variants of CACNA1A are associated with three allelic autosomal dominant conditions: episodic ataxias type 2, spinocerebellar ataxia type 6, and familial hemiplegic migraine type 1 [18]. Other paroxysmal disorders, including benign paroxysmal torticollis of childhood, benign paroxysmal tonic upward gaze, and epilepsy, are also associated with CACNA1A mutations [8].

Patients with episodic ataxia type 2 usually experience intermittent episodes of ataxia and nystagmus that can last from minutes to days during childhood or early adulthood [8,72]. It usually develops with dysarthria, tinnitus, dystonia, hemiplegia, and headache with the frequency of attacks varying from once or twice a year to three or four times a week [73]. Typically, exertion, stress, heat, fever, alcohol, caffeine, or drugs, such as phenytoin, can trigger these episodes [73]. Myokymia (fine twitching or rippling of muscle) is absent on physical examination or electromyographic studies [59]. Episodic ataxia type 2 attacks can be interrupted or reduced in frequency and severity by acetazolamide or 4-aminopyridine administration [73]. Few patients have epileptic encephalopathy with generalized absence or focal seizures with or without generalized tonic-clonic seizures and/or intellectual disabilities [18,74].

About half of families with familial hemiplegic migraine have heterozygous pathogenic missense variants in CACNA1A, which are called familial hemiplegic migraine type 1 [73]. Episodic hemiplegia occurs with one or more sensory auras such as hemianopsia,
hemisensory deficit, or aphasia in familial hemiplegic migraine type 1 [73].

Benign paroxysmal torticollis of childhood is a rare paroxysmal disorder characterized by recurrent episodes of head tilt accompanied by general symptoms that remit spontaneously [75]. The rare association with gain-of-function and loss-of-function CACNA1A mutations has been reported [75].

Benign paroxysmal tonic upward gaze was initially described as a benign phenomenon with negative investigations and eventual complete resolution of symptoms [76]. Later publications demonstrated that a similar clinical feature may arise from structural brain lesions, channelopathies, neurotransmitter disorders, and epileptic seizures [76]. CACNA1A mutations were detected in infants and young children with benign paroxysmal tonic upward gaze especially if associated with developmental delay, cerebellar signs, and other types of paroxysmal events [76].

Patients with CACNA1A mutations experience a high rate of different seizure types, involving febrile seizures, epileptic encephalopathy, generalized absence seizure, and focal seizures with or without generalized tonic-clonic seizures [18].

Pathological manifestations are explained by the synaptic dysfunction caused by the loss of Cav2.1 channels in particular cell types [77-79]. In conditional mutant mice, selective deletions of CACNA1A in cerebellar granule cells or Purkinje cells reduce the excitatory drive and neurotransmitter release, which cause ataxia and dyskinesia [80,81]. While GABA release is impaired, generalized epilepsy in cortical and hippocampal GABAergic interneurons [77].

2) KCNA1
Episodic ataxia type 1, which is also called ataxia with myokymia, is caused by heterozygous pathogenic variants in KCNA1, which encodes a potassium channel [82]. It is characterized by brief attacks (< 15 minutes) of ataxia and dysarthria that can occur up to 15 times per day [82]. Attacks can occur spontaneously or be triggered by anxiety, exercise, startle, and/or intercurrent illness [82]. Onset typically occurs in late childhood and early adolescence, and symptoms usually remit during the second decade [83]. Between attacks, widespread myokymia of the face, hands, arms, and legs occur. Electromyographic studies reveal myokymia, so called neuromyotonia [82]. Phenytoin can control symptoms; acetazolamide is also effective [84].

Episodic ataxia type 1 may be associated with epilepsy as tonic-clonic and focal seizures, one isolated episode of photosensitive epilepsy [85], as well as symptoms, such as head-turning, eyes deviating to the same side, flickering eyelids, lip-smacking, apnea, and cyanosis, have been reported [86]. Prolonged episodes of more than 30 minutes have been reported in individuals with severe early-onset epilepsy, albeit without the typical ataxia [87].

The molecular mechanisms of episodic ataxia type 1 are described as impaired channel function and reduced outward K+ flux through the channel [85,88]. In a mouse model of episodic ataxia type 1, altered motor performance and impaired cerebellar GABAergic transmission from the basket cells to the Purkinje cells was found [89], resulting in spontaneous myokymic activity, which was exacerbated by fatigue, ischemia, and low temperature [90]. However, although a similar phenomenon to the spread of acidification in the cerebellar cortex has been described, the causes of triggering the paroxysms of ataxia remain unknown [91].

Conclusion
Several genetic disorders were identified as co-occurrences of epilepsy and paroxysmal dyskinesias. Disease and associated genes are as follows: (1) PKD: PRRT2, SCN8A, SLC16A2, CHRNA4; (2) PNKD: CACNA1A, KCNMA1; (3) PED: SLC2A1, TBC1D24; (4) hemiplegic migraine: PRRT2, CACNA1A, SCN1A, ATP1A2; and (5) episodic ataxia: PRRT2, CACNA1A, KCNA1. These conditions are divided into three pathomechanisms: (1) channelopathy: SCN8A, CACNA1A, KCNMA1, SCN1A, KCNA1; (2) synaptopathy: PRRT2, CHRNA4, TB-CID24; and (3) transportopathy: SLC16A2, SLC2A1, ATP1A2.

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

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Author contribution
Conceptualization: TSK. Data curation: HA. Formal analysis: HA. Methodology: TSK. Project administration: TSK. Visualization: HA. Writing—original draft: HA. Writing—review & editing: TSK.

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Short Course and Early Switch of Vigabatrin for Infantile spasms

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Purpose: Vigabatrin has proven efficacy in the treatment of infantile spasms, but it carries the risk of irreversible visual field constriction. The incidence of vigabatrin-induced visual field constriction seems to depend on the extent of vigabatrin exposure. The aim of this study was to evaluate whether the therapeutic effect of vigabatrin is maintained in patients with infantile spasms receiving a short vigabatrin course followed by switching to another antiepileptic drug.

Methods: Patients with infantile spasms responsive to initial vigabatrin treatment were divided into a vigabatrin switch group (n=25) and a vigabatrin maintenance group (n=41). In the former group, vigabatrin was switched to other drugs within 6 months of spasm remission. The rate of seizure recurrence at 6 and 12 months from spasm remission was compared between the two groups.

Results: No statistically significant differences were found between the vigabatrin switch and maintenance groups in the age of onset, presence of concomitant seizures, time from spasm onset to vigabatrin treatment, time from vigabatrin treatment initiation to spasm remission, or vigabatrin dose at spasm remission. The number of patients with seizure recurrence at 12 months after spasm remission was 3 (3/25, 12%) in the vigabatrin switch group and 10 (10/41, 24.4%) in the vigabatrin maintenance group. The seizure recurrence rate at 12 months from spasm remission was not significantly different between groups.

Conclusion: A short course of vigabatrin could be considered in patients with infantile spasms who are responsive to initial vigabatrin treatment, since spasm remission was maintained after switching to other drugs.

Keywords: Spasms, infantile; Vigabatrin; Visual fields
Introduction

Vigabatrin (VGB) has proven efficacy in the treatment of infantile spasms that is resistant to conventional antiepileptic drugs (AED) [1]. No difference in long-term outcome was found between treatment with VGB or with adrenocorticotropic hormone (ACTH) [2-4]. Considering the serious side effects of ACTH such as infection, hypertension, osteoporosis, or electrolyte disturbances, VGB is a good choice for the treatment of infantile spasms [5,6].

However, VGB has risk of visual field constriction (VFC) as an adverse effect. Of the patients treated with VGB, 44% (738/1,678) had VFC [7]. VGB-induced visual field defect is irreversible, and its incidence increases with the duration and total dose of VGB [8,9]. In a study examining the visual fields in school age children who had received VGB in infancy, visual field defects were found in 9% of children who received VGB for 1 year or less, in 30% of children who received VGB for 12 to 24 months, and in 63% of children who received VGB for more than 2 years [10]. In an observational cohort study using electroretinogram (ERG) to assess the VGB-induced retinal toxicity, 5.3% and 13.3% of children developed retinal damage with 6 and 12 months of VGB treatment [11].

Patients receiving VGB treatment require regular visual field examination; however, perimetry is impossible in young children or in children with cognitive impairment. ERG, which can monitor the retinal toxicity in young children, is difficult to perform because it requires general anesthesia [12].

Since the incidence of VFC depends on the duration of VGB treatment, if we use a short-term VGB treatment paradigm, it will be possible to reduce the risk of VFC. Controlled studies on the optimal duration of VGB to maintain the therapeutic effect without adverse effect were not found. In a long-term (mean 5.25 years) follow-up of 21 patients with infantile spasms, three patients had relapse of spasms, all within the first 6 months [13]. In another study, VGB was stopped after 6 months without relapse in patients with infantile spasms with Down syndrome, cryptogenic etiology, or neonatal hypoxic-ischemic encephalopathy [14,15].

Although VGB is effective for the treatment of infantile spasms, the risk of irreversible adverse events increases with the duration of treatment. Hence, if the recurrence rate does not increase in patients with a short treatment course of VGB followed by switching to another AED when compared with patients with a long-term VGB treatment, it could be a new strategy for treating infantile spasms. The purpose of this study was to evaluate whether the recurrence rate increases after switching to another AED from VGB compared to long-term VGB treatment in patients with infantile spasms.

Materials and Methods

This study was approved by the Institutional Review Board of the Seoul National University Hospital (IRB No. H-1503-033-654). Written informed consent by the patients was waived due to a retrospective nature of our study.

Medical records of patients newly diagnosed with infantile spasms and treated with VGB in the Seoul National University Hospital from January 1997 through May 2014 were reviewed retrospectively. Infantile spasms were defined as the follows: (1) epileptic spasm onset during infancy at less than 12 months of age; (2) spasms confirmed either by history or by video electroencephalography (EEG) monitoring; and (3) hypsarrhythmic pattern on interictal EEG. Patient inclusion criteria included being a VGB responder and having a follow-up period of at least 12 months from spasm free. VGB responder was defined as (1) spasm free within 1 month of starting on VGB; (2) remaining spasm free for more than 1 month; and (3) resolution of hypsarrhythmic pattern on EEG. For the patients taking other AED before VGB start, patients without change of dose during were included. Patients with other additional AEDs after the start of VGB were excluded. Also, patients treated with corticosteroids were not included.

Gender, date of birth, age at spasms onset, etiology, EEG record, time from spasms onset to VGB treatment initiation, time from VGB treatment initiation to spasm free, VGG dose at spasm free, and relapse at 6 months and 12 months from spasm free were reviewed.

Patients were divided into two groups: VGB early switch group (switch group) and VGB maintenance group (maintenance group). VGB was switched with other drugs within 6 months of spasms remission in the VGB early switch group. The recurrence rate of spasms and other seizures at 6 and 12 months from spasms remission was compared between the two groups. In addition, risk factors such as gender, VGB switch, age of onset, etiology, and concomitant seizures were compared between patients who relapsed at 12 months and those who did not.

Statistical analysis was performed using SPSS version 22.0 for Windows (IBM Co., Armonk, NY, USA). A t-test for comparison of means and chi-square test or Fisher’s exact test for comparison of proportion between groups were used. Statistical significance was defined as $P < 0.05$.

Results

1. Baseline characteristics

Two hundred and three children were newly diagnosed with infantile spasms and treated with VGB between January 1997 and May
2014. Seventy patients were VGB responder, and 66 patients satisfied inclusion criteria. Two patients who had less than 12 months follow-up and two patients for whom VGB was switched with other drugs between 6 and 12 months of spasms remission were excluded.

Of the 66 patients included in the analysis, 25 patients (12 boys, 13 girls) were in the switch group, and 41 patients (24 boys, 17 girls) were in the maintenance group. The mean age of infantile spasms onset was 6.1 months in the switch group, and 5.8 months in the maintenance group (P = 0.562). The mean time between onset of spasms and initiation of VGB was 24.5 days in the switch group, and 35.2 days in the maintenance group (P = 0.243). The mean time between initiation of VGB and spasm free was 11.9 days in the switch group, and 13.5 days in the maintenance group (P = 0.476). The mean VGB dose at spasm free was 70.5 mg/kg/day in the switch group, and 64.9 mg/kg/day in the maintenance group (P = 0.451). Six patients in each group had concomitant seizures when spasms occur (P = 0.348).

The number of symptomatic cases was 12 (tuberosum sclerosis complex [TSC] two, congenital malformation one, brain injury eight, chromosome abnormality [Down syndrome] one) in the switch group, and 27 (TSC nine, congenital malformation seven, brain injury eight, central nervous system infection three) in the maintenance group.

The mean duration between spasm free and tapering VGB was 2.5 months (range, 0.5 to 5.0), and VGB was stopped after an average of 4.5 months (range, 1.4 to 7.5) from spasm free. In the switch group, VGB was replaced with zonisamide (n = 13), levetiracetam (n = 11), and topiramate (n = 1) (Table 1).

2. Outcome
At 6 months from spasm free, the number of patients with recurrence of spasm was two, and the number of patients with recurrence of other seizure was four (Table 2). At 12 months from spasm free, the number of patients with recurrence of spasm was six, and the number of patients with recurrence of other seizure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Switch (n = 25)</th>
<th>Maintenance (n = 41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>12 (48)</td>
<td>24 (59)</td>
<td>0.404</td>
</tr>
<tr>
<td>Mean age at onset (mo)</td>
<td>6.1</td>
<td>5.8</td>
<td>0.562</td>
</tr>
<tr>
<td>Mean time from IS to VGB (day)</td>
<td>24.5</td>
<td>35.2</td>
<td>0.243</td>
</tr>
<tr>
<td>Mean VGB dose when spasm-free (mg/kg/day)</td>
<td>11.9</td>
<td>13.5</td>
<td>0.476</td>
</tr>
<tr>
<td>Mean VGB dose at spasm free (mg/kg/day)</td>
<td>70.5</td>
<td>64.9</td>
<td>0.451</td>
</tr>
<tr>
<td>Concomitant seizures</td>
<td>6 (24)</td>
<td>6 (15)</td>
<td>0.348</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>12 (48)</td>
<td>27 (66)</td>
<td>0.152</td>
</tr>
<tr>
<td>TSC</td>
<td>2</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Congenital malformation</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Brain injury (HIE etc.)</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>CNS infection</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%).

Table 3. Seizure recurrence at 12 months after becoming spasm-free

<table>
<thead>
<tr>
<th>Spasm recurrence</th>
<th>Switch (n = 25)</th>
<th>Maintenance (n = 41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptogenic</td>
<td>0</td>
<td>6 (15)</td>
<td>0.075</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other seizure</td>
<td>3 (12)</td>
<td>4 (10)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

Table 4. Risk factors for seizure recurrence (at 12 months)

<table>
<thead>
<tr>
<th>Male sex</th>
<th>Recurrence (n = 13)</th>
<th>Remission (n = 53)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VGB switch</td>
<td>6 (46)</td>
<td>30 (57)</td>
<td>0.498</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>10 (77)</td>
<td>29 (55)</td>
<td>0.144</td>
</tr>
<tr>
<td>Mean onset age (mo)</td>
<td>6.1</td>
<td>5.8</td>
<td>0.685</td>
</tr>
<tr>
<td>Mean time from IS to VGB (day)</td>
<td>36.5</td>
<td>29.8</td>
<td>0.551</td>
</tr>
<tr>
<td>Mean time from VGB to becoming spasm-free (day)</td>
<td>13.3</td>
<td>12.8</td>
<td>0.856</td>
</tr>
<tr>
<td>Mean VGB dose when spasm-free (mg/kg/day)</td>
<td>59.2</td>
<td>69</td>
<td>0.275</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

IS, infantile spasms; VGB, vigabatrin.
was seven (Table 3). The average period from spasm free to recurrence was 8.4 months (range, 4.6 to 12.0), and the average period to other seizure recurrence was 6.0 months (range, 2.8 to 9.0).

3. Risk factors for seizure recurrence

After 12 months from spasms remission, 13 of 66 patients developed subsequent seizures: six patients had spasms and seven patients had other types of seizures. Clinical characteristics of patients by recurrence are shown in Table 4. There was no statistically significant difference between the recurrence group and the remission group. The number of patients in the switch group was three (23%) with recurrence and 22 (42%) without recurrence (P = 0.340). The number of symptomatic cases was 10 (77%) with recurrence and 29 (55%) without recurrence (P = 0.144). When patients who experienced recurrence at 12 months after spasms had controlled were compared to patients without recurrence, no statistically significant difference was found, but recurrence tends to occur more frequently in cases where the cause of spasms was symptomatic.

Discussion

VGB is effective in infantile spasms but can cause irreversible retinal toxicity manifested by VFC. Moreover, previous studies have reported that longer duration of medication increases the risk of retinal toxicity [8-10]. Recent research has shown that there is a difference in the frequency of visual field defect at 6 months after VGB medication and that after 12 months [11]. This indicates that vision loss can occur even if treatment has not been prolonged for years. However, there is a lack of research on the duration of medication to maintain therapeutic effects without increasing the risk of an adverse effect. In a study, VGB was stopped after 3 to 6 months in 19 patients who were responding to VGB. There was no case of recurrent spasms, although follow-up duration was not long, 13 to 50 months [14]. However, in a study on long-term prognosis, there was more than 50% recurrence in the form of epilepsy, including partial seizures [3,16]. So, it is often required treatment for subsequent seizure after the spasm remission. For infantile spasms patients who were successfully treated with VGB, short term VGB with followed another AED may be considered. If the recurrence rate does not increase after switching to another AED compared to long-term VGB treatment, it could be a new treatment strategy that reduces the risk of VFC and maintains the therapeutic effect.

We changed the medication to a different anticonvulsant drug in infantile spasms patients who were successfully treated with VGB within 6 months, and compared these patients to those who continued VGB, for any difference in the recurrence rate of spasms and other seizures. Although there is no guideline for the optimal treatment duration of VGB, limited studies suggest VGB could be stopped after 6 months without a relapse [14,15] and incidence of VFC seems to increase after 6 months of VGB treatment [11]. There was no statistically significant difference between the two groups with respect to baseline characteristics and recurrence rate at 6 and 12 months after spasms controlled.

Although no medications have been proven to be effective for infantile spasms except for ACTH and VGB, there are cases where infantile spasms were treated with medications that are effective for partial seizures, such as topiramate, zonisamide, and levetiracetam [17-22]. More than 50% of the patients with a history of infantile spasms develop chronic epilepsy, most of them have other types of seizures than spasms. AED that is effective for concomitant with spasms or other types of seizures that appear after infantile spasms is controlled should be considered as switch drug.

This study is a retrospective study, and has limitations in that the duration of VGB treatment and the switch in drug were not constant in the switch group and the follow-up period was short. However, our data suggest that short course of VGB followed by switching to another AED can be a new strategy for treating infantile spasms. In future research, long-term prognosis and the difference in frequency of VFC between the two groups should be assessed.

Conflicts of interest

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

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Conceptualization: HWR, BCL, and KJK. Data curation: HWR and BCL. Formal analysis: HWR and BCL. Methodology: HWR, BCL, and KJK. Project administration: HWR, BCL, and KJK. Visualization: HWR, BCL, and KJK. Writing - original draft: HWR and KJK. Writing - review & editing: HWR, HK, BCL, HH, JHC, JEC, and KJK.

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1. Carmant L. Vigabatrin therapy for infantile spasms: review of major trials in Europe, Canada, and the United States; rec-
Purpose: We aimed to assess the efficacy and safety of lacosamide in Korean adolescents with Lennox-Gastaut syndrome (LGS), especially in those who concomitantly used other sodium channel blockers (SCBs).

Methods: We retrospectively reviewed the medical records of adolescents with LGS who initiated lacosamide from ages 16 to 18. The efficacy of lacosamide was evaluated by seizure frequency before and after lacosamide trial. Safety was assessed by lacosamide-related adverse events, consequent dosage titration, and titration effects. We compared the efficacy and safety of lacosamide according to concomitant use of other SCBs.

Results: In 26 eligible adolescents with LGS, the median age of seizure onset was 2.0 years, and the median age of lacosamide initiation was 17.1 years. At the time of lacosamide initiation, the median number of concomitant antiepileptic drugs was 4, and 23 patients (88%) had tried dietary, surgical, or neuromodulatory therapies. Patients were on lacosamide for a median of 13.5 months with a median maximal dosage of 8.1 kg/m²/day. After lacosamide trial, 11 patients (42%) had an over 50% reduction of seizures. Six patients (23%) had lacosamide-related adverse events. The percentage of patients on concomitant SCBs was higher among non-responders (10 of 15, 67%) than among responders (6 of 11, 55%). Patients taking concomitant SCBs had a higher ratio of adverse effects (5 of 16, 31%) than their counterparts (1 of 10, 10%).

Conclusion: Lacosamide is an effective and tolerable antiepileptic drug in adolescents with LGS. Concomitant SCB use may lead to less effective treatment and more adverse events.

Keywords: Lacosamide; Lennox Gastaut syndrome; Epilepsy; Sodium channel blockers
ized paroxysmal fast activities. About 1% to 2% of epilepsy patients are diagnosed with LGS [1]. Seizures are often resistant to diverse medications and adjuvant therapies such as ketogenic diet, corpus callosotomy, resective surgery, or vagus nerve stimulation (VNS) [2].

Lacosamide (LCM) is an antiepileptic drug (AED) which augments slow inactivation of voltage-gated sodium channels and stabilizes neuronal membrane [3]. The medication was initially approved for treatment of focal (partial-onset) epilepsy for patients over 16 years (Europe, Korea) or 17 years old (United States). The novel mechanism of LCM led to research on efficacy of LCM for seizure control in patients with focal epilepsy and drug-resistant epilepsy, including pediatric patients. Several research centers investigated possible interaction between LCM and other AEDs with sodium channel blocking properties, showing mixed results.

Since the United States Food and Drug Administration (US-FDA) approved of pediatric LCM use recently in 2017, there are limited data on treatment of LCM on LGS patients. We aimed to assess the efficacy and safety of LCM on Korean adolescent LGS population in a single tertiary center. Because most LGS patients are on multiple AEDs including sodium channel blockers (SCBs), we also sought to assess the effect of LCM and concomitant use of other SCBs.

Materials and Methods

We performed a retrospective study of 26 patients who were diagnosed with LGS and started LCM as adjuvant antiepileptic medication at a single tertiary referral center between March 2014 and June 2019. We initially reviewed medical records of 53 adolescents who were diagnosed with LGS and tried LCM. Among them, we filtered 36 patients who started LCM from age 16 to 18. We excluded four patients who maintained LCM for less than 3 months, one patient who had tuberectomy at 2 months after LCM add-on, which may blur the effect of LCM, and five patients who had incomplete information on seizure frequency before or after LCM use, leaving 26 patients who maintained LCM and visited the clinic for at least 3 months after LCM add-on. Review of medical records was done from September 2019 to December 2019.

Patients were diagnosed with LGS by clinical symptoms and EEG. They had intellectual disability and drug-resistant epilepsy with multiple semiology. EEG at initial diagnosis showed patterns of slow and disorganized background with multifocal sharp wave discharges, generalized slow spike wave discharges and/or generalized paroxysmal fast activities [1].

For etiologic evaluation, all patients had gone through brain magnetic resonance imaging (MRI). If there was no clinical history of possible acquired etiology, targeted gene panel for epilepsy comprising 172 genes related to epilepsy had been tested.

Other clinical history included age, sex, seizure semiology, frequency and intensity, and previous treatment before LCM initiation. Adjuvant treatment comprised of ketogenic diet, VNS, or epilepsy surgeries including corpus callosotomy, disconnection, or resection of possible lesion. We noted concomitant AEDs including other SCBs.

Patients had started LCM from daily dosage of 1.5 to 4 mg/kg divided in two doses. Dosage had been titrated up to 12.5 mg/kg/day at most, not exceeding 600 mg/day. All patients visited the clinic over 6 months after LCM add-on. Every 3 to 6 months, we checked seizure frequency, intensity and drug-related adverse events. We defined ‘responders’ as patients whose seizure frequency decreased more than 50% of baseline after taking LCM for 3 months. If adverse events related to LCM were not negligible, slow titration, transient tapering, or transient discontinuation was done. After symptoms subsided, dosage was gradually resumed.

Statistic evaluation was done with chi-square tests, exact Fisher’s tests, and Mann-Whitney U tests using SPSS version 23.0 (IBM Co., Armonk, NY, USA). This study was approved by Institutional Review Board (IRB) in Severance hospital, Seoul, Korea (IRB protocol number 4-2020-0292). Written informed consent by the patients was waived due to a retrospective nature of our study.

Results

Our study included 26 adolescents diagnosed with LGS (Table 1). Among them, 17 patients were male (65%). Patients had seizure onset at median 2.0 years of age (interquartile range [IQR], 0.7 to 4.3). Most common etiology was congenital structural, found in seven patients (27%) with focal cortical dysplasia, heterotopia, and pachygyria (Table 1). Six patients (23%) had acquired structural etiology of periventricular leukomalacia, traumatic brain injury, injury after chemotherapy and radiotherapy, and hypoxic injury after a major operation. Six patients had infectious etiology (23%) which presented as encephalitis, bacterial meningitis and neonatal sepsis. One patient (4%) had genetic etiology of ZEB2 gene mutation. The remaining six patients (23%) had no etiology found after extensive work-up.

Patients added LCM at median 17.1 years of age (Tables 1 and 2). At LCM initiation, patients were on median four antiepileptic medications (IQR, 3 to 4). A majority of 23 patients (88%) tried adjunctive therapies. Among them, 18 patients (69%) had tried ketogenic diet or modified Atkins’ diet. While 16 patients had stopped dietary therapies mostly due to lack of seizure control, poor compliance, or onset of systemic or gastrointestinal disease, two patients were still on modified Atkins’ diet at the time of LCM.

[Table 1]

- Numbers and percentages for etiology of LGS

[Table 2]

- Summary of clinical characteristics

https://doi.org/10.26815/acn.2020.00080
Table 1. Baseline demographics in adolescents with Lennox-Gastaut syndrome (n=26), and comparison between lacosamide responders and non-responders: onset, etiology, treatment history, and lacosamide treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Seizure control 50%–99% (n = 11)</th>
<th>Seizure control &lt; 50% (n = 15)</th>
<th>Total (n = 26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female (ratio)</td>
<td>7/4 (64:36)</td>
<td>10/5 (67:33)</td>
<td>17/9 (65:35)</td>
<td>1.000</td>
</tr>
<tr>
<td>Age of seizure onset (yr)</td>
<td>2.0 (0.5–3.0)</td>
<td>3.0 (0.7–7.0)</td>
<td>2.0 (0.7–4.3)</td>
<td>0.526</td>
</tr>
<tr>
<td>Etiology (n/subgroup)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural (congenital)</td>
<td>2/11 (18)</td>
<td>5/15 (33)</td>
<td>7 (27)</td>
<td>0.658</td>
</tr>
<tr>
<td>Structural (acquired)</td>
<td>2/11 (18)</td>
<td>4/15 (27)</td>
<td>6 (23)</td>
<td>1.000</td>
</tr>
<tr>
<td>Genetic</td>
<td>1/11 (9)</td>
<td>0/15 (0)</td>
<td>1 (4)</td>
<td>0.423</td>
</tr>
<tr>
<td>Infection</td>
<td>4/11 (36)</td>
<td>2/15 (13)</td>
<td>6 (23)</td>
<td>0.348</td>
</tr>
<tr>
<td>Unknown</td>
<td>2/11 (18)</td>
<td>4/15 (27)</td>
<td>6 (23)</td>
<td>1.000</td>
</tr>
<tr>
<td>Seizure type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal only</td>
<td>2/11 (18)</td>
<td>7/15 (47)</td>
<td>9 (35)</td>
<td>0.217</td>
</tr>
<tr>
<td>Generalized</td>
<td>3/11 (27)</td>
<td>5/15 (33)</td>
<td>8 (31)</td>
<td>0.658</td>
</tr>
<tr>
<td>Focal and generalized</td>
<td>6/11 (55)</td>
<td>3/15 (20)</td>
<td>9 (35)</td>
<td>0.103</td>
</tr>
<tr>
<td>Concomitant AEDs</td>
<td>4 (3–5)</td>
<td>4 (3–4)</td>
<td>4 (3–4)</td>
<td>0.797</td>
</tr>
<tr>
<td>Previous dietary, neuromodulatory, or surgical treatment (n/subgroup)</td>
<td>10/11 (91)</td>
<td>13/15 (87)</td>
<td>23 (88)</td>
<td>1.000</td>
</tr>
<tr>
<td>Prior KD</td>
<td>7/11 (63)</td>
<td>11/15 (73)</td>
<td>18 (69)</td>
<td>0.683</td>
</tr>
<tr>
<td>Prior VNS</td>
<td>3/11 (27)</td>
<td>7/15 (47)</td>
<td>10 (38)</td>
<td>0.428</td>
</tr>
<tr>
<td>Prior epileptic surgery</td>
<td>5/11 (45)</td>
<td>7/15 (47)</td>
<td>12 (46)</td>
<td>0.951</td>
</tr>
<tr>
<td>Age at LCM initiation (yr)</td>
<td>17.1 (16.7–17.6)</td>
<td>17.3 (16.6–17.9)</td>
<td>17.1 (16.7–17.9)</td>
<td>0.511</td>
</tr>
<tr>
<td>Maximum LCM dose (mg/kg/day)</td>
<td>8.0 (6.9–10.0)</td>
<td>7.8 (6.5–9.8)</td>
<td>8.1 (6.8–9.8)</td>
<td>0.701</td>
</tr>
<tr>
<td>Duration of LCM (mo)</td>
<td>21.0 (12.0–30.0)</td>
<td>11.0 (7.0–15.0)</td>
<td>13.5 (7.8–22.5)</td>
<td>0.026</td>
</tr>
<tr>
<td>LCM discontinuation</td>
<td>0</td>
<td>7 (47)</td>
<td>7 (27)</td>
<td>0.010</td>
</tr>
<tr>
<td>Concomitant SCB(s)</td>
<td>6 (55)</td>
<td>10 (67)</td>
<td>16 (62)</td>
<td>0.689</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or number (%).
AED, antiepileptic drug; KD, ketogenic diet; VNS, vagus nerve stimulation; LCM, lacosamide; SCB, sodium channel blocker.

add-on. Also, 10 patients (38%) had VNS, and 12 patients (46%) went through epileptic surgeries including corpus callosotomy, disconnection or resection.

Patients were on LCM for median 13.5 months (IQR, 7.8 to 22.5). After dosage titration, patients’ maximum dose was median 8.1 mg/kg/day (IQR, 6.8 to 9.8). Among 26 patients, 22 patients (85%) continued LCM over 6 months. Eleven patients (42%) had seizures decreased over 50% after LCM initiation (Fig. 1). There was no case of seizure freedom.

Among 15 non-responders, eight patients maintained LCM until last visit, for median 15 months (IQR, 11.5 to 21.5). Seven patients withdrew LCM after median 7 months (IQR, 3 to 9) of LCM administration because of poor seizure control, including one patient who had more frequent seizures after LCM add-on. The patient with worsening seizures was a 17-year-old boy who was born at term without perinatal history. He had delayed speech onset at 3 years old, could not walk independently, and started head drop seizures at 11 years old. Brain MRI showed mild enlargement of the ventricles with white matter thinning, suggestive of periventricular leukomalacia. EEG at 17 years of age showed generalized slow spike-waves, and he started LCM while taking topiramate and levetiracetam. He had average 10 head drop seizures noted every week at time of LCM add-on, but after 3 months, he had over 20 weekly seizures.

There was no statistical difference in the previous treatment history and LCM treatment profile between the responders and non-responders (Table 1). Both groups of 11 responders and 15 non-responders to LCM had early onset of seizures, the responders at median age 2.0 years old (IQR, 0.5 to 3.0) and non-responders at age 3.0 years old (IQR, 0.7 to 7.0). Both groups started LCM at median age 17.1 years old and were on median four antiepileptic medications including valproate, clobazam, perampanel, and/or SCBs such as lamotrigine, carbamazepine or oxcarbazepine at LCM initiation. Most commonly used AEDs were valproate and lamotrigine (each 14 patients, 54%), followed by clobazam (10 patients, 38%).

Higher ratio of non-responders had tried adjunctive therapies compared to responders. Eleven out of 15 non-responders (73%) had tried ketogenic diet compared to seven out of 11 responders (64%). Seven of 15 non-responders (47%) had VNS insertion.
Table 2. Effects of other sodium-channel blockers in the treatment of seizures with lacosamide and lacosamide-related adverse events

<table>
<thead>
<tr>
<th>Variable</th>
<th>SCB (+)</th>
<th>SCB (–)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>16 (62)</td>
<td>10 (38)</td>
<td>-</td>
</tr>
<tr>
<td>Responders/subgroup</td>
<td>6/16 (38)</td>
<td>5/10 (50)</td>
<td>0.689</td>
</tr>
<tr>
<td>LCM-related AEs (n/subgroup)</td>
<td>5/16 (31)</td>
<td>1/10 (10)</td>
<td>0.352</td>
</tr>
<tr>
<td>LCM transiently decreased or discontinued after AE</td>
<td>1</td>
<td>1</td>
<td>1.000</td>
</tr>
<tr>
<td>LCM decreased or discontinued for the rest of the study after AE</td>
<td>2</td>
<td>0</td>
<td>0.508</td>
</tr>
</tbody>
</table>

Clinical manifestation of LCM-associated AEs

- Hyperactivity, inattention: 1 vs 1; P = 1.000
- Somnolence: 1 vs 0; P = 1.000
- Ataxia: 1 vs 0; P = 1.000
- Emesis: 2 (1) vs 0; P = 0.508

Values are presented as number (%).
SCB, sodium channel blocker; LCM, lacosamide; AE, adverse event.

a Transient LCM reduction or discontinuation after onset of the adverse event; b LCM reduction or discontinuation for the rest of the study period after onset of the adverse event.

Fig. 1. Patients' response to lacosamide (LCM) based on LCM dosage per body weight. After dosage titration, patients' maximum dose ranged from 2.6 to 12.5 mg/kg/day (median, 8.1 [interquartile range, 6.8 to 9.8 mg/kg/day]). There was no significant difference in dosage per body weight.

Fig. 2. Patients' response to lacosamide based on etiology. There was no statistically significant difference in the response or withdrawal rate according to etiology.

compared to three of 11 responders (27%). Half of the patients in both groups had gone through epileptic surgeries before LCM trial (five of 11 responders [45%] and seven of 15 non-responders [47%], respectively). Responders had median maximum-LCM-to-body-weight ratio of 8.0 mg/kg/day (IQR, 6.9 to 10.0) and non-responders had median ratio of 7.8 kg/mg/day (IQR, 6.5 to 9.8).

There was no statistically significant difference in efficacy of LCM among all etiologic categories (Table 1, Fig. 2). The patient with ZEB2 gene mutation responded to LCM. Among six patients with infectious causes, four patients responded to LCM. One-third of the patients responded to LCM in the groups with congenital structural, acquired structural, and unknown origin (two patients each). On the other hand, three out of seven patients with congenital structural origin responded to LCM.
tual structural lesions withdrew from LCM due to poor seizure control. Two out of six patients with acquired structural lesions, one patient with infectious etiology and one patient with unknown etiology also stopped LCM because of little effect.

Among 11 responders, six patients (55%) were on other SCBs such as lamotrigine, carbamazepine, or oxcarbazepine at the time of LCM add-on. On the other hand, 10 out of 15 non-responders (66%) were on SCBs. There was no patient with phenytoin during LCM trial.

LCM-related adverse events were noted in six patients (23%) (Table 2). There were two cases of behavioral changes such as hyperactivity and inattention, and two cases of emesis. Other two cases were somnolence and ataxia. Two patients required transient decrease or discontinuation of LCM, but resumed the dosage after symptoms subsided. Two non-responders, one with somnolence and another with ataxia, reduced LCM for the rest of the study period. No patient discontinued LCM solely because of adverse events.

There were five cases of adverse events in 16 patients with concomitant SCBs (27%) (Table 2). In the two cases of somnolence and ataxia, LCM was decreased for the rest of the study period. Also, in another case of emesis, LCM was transiently discontinued. In 10 patients without concomitant SCBs, there was only one case of adverse event (18%). The patient had emesis, and had transient reduction of LCM. The results were statistically insignificant.

Discussion

Since the US-FDA and European Commission (EC) approved of LCM in 2008 for treatment of epilepsy in patients 16 years (EC) or 17 years (US-FDA) older [3], previous studies on LCM reported its efficacy and safety on focal epilepsy or drug-resistant epilepsy mainly in adults. However, due to the medication’s unprecedented mechanism of sodium-channel blocking effect by enhancing slow activation of voltage-gated sodium channels, pediatric neurologists cautiously scrutinized its effects on drug-resistant epilepsy [4-6]. Guilhoto et al. [4] reviewed LCM treatment in 16 pediatric patients and found six responders (37.5%) with four cases (25%) of non-severe adverse events which prompted the discontinuation of LCM. Grosso et al. [6] performed a prospective multi-center study of LCM use in 24 pediatric patients with focal epilepsy under age 4 and found 10 responders after 3 months of LCM (42%), including four patients who became seizure free (17%). After 12 months, four patients (22%) were still responding to LCM. Adverse effects were non-severe and found in eight patients (33%) [6]. In light of accumulating reports on pediatric population, in 2017, the US-FDA allowed of extrapolating oral LCM use for treatment of focal epilepsy on pediatric population aged 4 and older [7].

Since LGS has onset age at childhood, there were scarce studies on LGS before the recent FDA allowance of LCM. Rastogi and Ng [5] prospectively studied efficacy of LCM on 16 pediatric patients, including those with diagnosis of LGS. Among the four LGS patients, two patients had seizures decreased over 90%, and two patients had no effect [5]. Andrade-Machado et al. [8] reported a case of 20-year-old LGS patient who had seizures and EEG patterns worsened after LCM usage and returned to baseline after its discontinue. Grosso et al. [9] suggested possible efficacy of LCM on a multi-center retrospective study of 18 children with LGS, of whom six patients (33%) responded to LCM. Miskin et al. [10] reported efficacy of LCM on 21 pediatric patients with drug-resistant generalized epilepsy, eight of whom had LGS, and seven of the eight patients (87.5%) responded to LCM.

Our study includes 26 patients with LGS, the largest cohort of adolescents with LGS who tried LCM. In our cohort, 11 of 26 patients (42%) responded to LCM, which is comparable to above previous reports of variable drug response in LGS which ranged from 33% to 88% [5,9,10]. There was no case of seizure freedom, which is consistent with the three studies. Adverse effects were noted on six patients (25%), which were not severe. This result is less than previous report of non-severe adverse events of 44% in LGS [9], and results of other pediatric studies, which ranged from 29% [10] to 51% [11].

Whether LCM and SCBs work synergistically or additively remains unknown. The fact that LCM enhances slow inactivation of voltage-gated sodium channels, while other SCBs act on fast inactivation [12] suggest that these drugs may work synergistically. However, previous studies have been controversial, and some were against the concomitant use of SCBs and LCM. A study on 158 epilepsy patients with mean age of 42.1 years demonstrated higher efficacy and lower adverse events in patients without concomitant SCBs compared to patients with concomitant SCBs [13]. A more recent study evaluated LCM retention rates in 223 pediatric drug-resistant epilepsy patients, and found that LCM treatment failure was correlated with concomitant treatment of SCBs [14]. On the other hand, one study noted that among 21 pediatric patients with focal epilepsy treated with LCM, there was no significant difference in efficacy or adverse effects between those with simultaneous use of SCBs and others without SCBs [15].

Although statistically insignificant, the results of our study suggest possible interaction of LCM with concomitant SCBs. More patients without concomitant SCBs responded to LCM (six out of 11, 55%) compared to patients with concomitant SCBs (five out of 15, 33%). Patients without other SCBs also had lower percentage of adverse effects (1 of 10, 10%) compared to those with other
SCBs (five of 16, 31%). Also, more patients with concomitant SCBs had adverse events requiring LCM decrease during the rest of study period (two cases), or transient discontinuation of LCM (one case), compared to only one case in non-SCB group presenting emesis who had transient reduction of LCM.

The mechanisms of the possible interaction between LCM and other SCBs are under investigation. The report that plasma concentrations of lamotrigine and oxcarbazepine were not affected by concomitant LCM use suggest that effects of LCM on these drug concentrations is minimal [16]. Another report indicates a low potential for pharmacokinetic drug-drug interaction between LCM and carbamazepine [17]. Novy et al. [18] suggested there may be pharmacodynamic interaction between LCM and SCBs, as the AED levels do not change during the intolerable adverse events. Further studies would give more precise guideline on prescription of LCM and other SCBs.

Our study adds to rare studies specifying LCM use in pediatric LGS population. Because patients with drug-resistant epilepsy are on hardship of taking multiple AEDs usually twice a day, our information on concomitant SCB use may prevent some patients from excessive periods of inefficacy and intolerability by LCM and concomitant SCBs. However, our data is based on retrospective chart review, so some of the medical records may not contain information on efficacy or adverse effects of LCM. We could include a small number of 26 patients due to low prevalence of LGS in adolescents and short period of LCM use in pediatric patients, and a larger cohort may enable a statistically significant evaluation. We evaluated patient response at 3 months of LCM use, but since patients with drug-resistant epilepsy take AEDs for years, more information on long-term use could give pragmatic clinical information. Although our patients took oral tablets of LCM which were the only option in Korean market during the study period, further studies on intravenous LCM use in pediatric patients may help them in cases when they cannot tolerate oral medications or when they need fast activation of the medication.

In conclusion, LCM is an effective and tolerable medication for seizure control in adolescents with LGS. Concomitant use of SCBs could lead to decreased effect or increased adverse events of LCM. Further studies on LCM in pediatric population could enhance proper treatment with LCM in LGS patients.

**Conflicts of interest**

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

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**Author contribution**

Conceptualization: SHK and HDK. Data curation: HSC, HCK, and HDK. Formal analysis: HSC and SHK. Methodology: HSC and SHK. Project administration: HSC, SHK, and JSL. Visualization: HSC and SHK. Writing - original draft: HSC. Writing - review & editing: HSC, SHK, HCK, JSL, and HDK.

**References**

11. Pasha I, Kamate M, Didagi SK. Efficacy and tolerability of lacos-
Purpose: Multiple independent spike foci (MISF) have been reported to be associated with hypsarrhythmia and slow spikes and waves. However, some patients with MISF demonstrate a good prognosis, such as benign focal epilepsy. This study aimed to elucidate the prognosis of epileptic children with MISF and to analyze the prognostic factors.

Methods: The subjects were 115 epileptic children aged 1 to 18 years who visited Pusan National University Children’s Hospital between November 2008 and July 2016 and in whom MISF were noted on electroencephalography. We excluded patients with infantile spasms, congenital metabolic diseases, neurodegenerative diseases, or post-encephalitic epilepsy. We retrospectively reviewed participants’ clinical information. Seizure control was defined as no seizures over 6 months at the last visit. Prognostic factors were analyzed in the seizure control (group A; 84 [73%]) and no seizure control (group B; 31 [27%]) groups.

Results: Generalized seizure (P=0.033), intellectual disability (P<0.001), cerebral palsy (P=0.046), and abnormal background activity and electrodecrements on electroencephalography (P<0.001) were significantly more common in group B. No clinically significant abnormalities were noted on magnetic resonance imaging of the brain. The MISF improved on follow-up electroencephalography in 58 (71.6%) patients in group A versus 10 (35.7%) in group B (P=0.002).

Conclusion: Despite MISF on electroencephalography, two-thirds of patients had a benign clinical course, particularly those with post-infantile epilepsy and no infantile spasms. The prognostic factors of poor outcomes were generalized seizures, intellectual disability, and abnormal background activity on electroencephalography.

Keywords: Child; Electroencephalography; Epilepsy; Prognosis
Introduction

Historically, in the 1970s, the presence of multiple independent spike foci (MISF) on electroencephalography (EEG) was considered findings associated with hypsarrhythmia and slow spike and wave complexes, which were remarkable findings of infantile spasms and Lennox-Gaustaut syndrome (LGS) [1-3]. Blume [4] also described it was highly associated with intellectual abnormality despite a lack of infantile spasms or LGS. Thereafter, numerous studies on epileptic syndrome, infantile spasms, and LGS have led to their being widely accepted as epileptic syndromes distinctive from others; however, a few recent studies have aimed to reassess the significance of MISF in epilepsy.

Several recent studies proposed that patients for whom MISF are seen on EEG along with some characteristic clinical findings, who had poor prognosis and poor clinical course might be reclassified as having so-called severe epilepsy with MISF (SE-MISF) [5,6]. Nevertheless, it were not widely accepted yet and in the clinical setting, cases with unfavorable prognosis as well as favorable outcome despite MISF have been documented similar to those of patients with benign focal epilepsy. Here we aimed to analyze the prognosis of patients with post-infantile epilepsy with MISF and the prognostic factors associated with seizure control.

Materials and Methods

1. Patients and method

This retrospective study included pediatric patients aged 1 to 18 years who underwent an EEG study at the Pediatric Neurology clinic at Pusan National Children’s Hospital between November 1, 2008 and July 31, 2016. All subjects were patients with epilepsy diagnosed by the Department of Neurology. The study population included 68 male patients and 47 female patients (ratio, 1.45:1). The mean onset age was 31 months at the last visit by June 31, 2017. The patients with seizure control were identified in the seizure control group (group A), while those without seizure control were in the no seizure control group (group B). The groups were compared to identify the prognostic factors influencing the therapeutic result.

Clinical information included sex, age at seizure onset, age at EEG study showing MISF, birth history such as gestational age and perinatal problems, and family history of epilepsy or febrile convulsions. The seizure profiles that were related to a history of seizures included seizure type, status epilepticus, duration between first seizure and start of anti-epileptic drug (AED) therapy, seizure frequency during the most recent 3 months from the identification of MISF on EEG. Comorbid conditions included intellectual disability (developmental delay in early childhood, including a speech-language delay), autism spectrum disorder, cerebral palsy, genetic disorder, and lesions suspiciously associated with epilepsy on magnetic resonance imaging (MRI). Other abnormal EEG findings were also analyzed, including abnormal background activities, focal slow waves, and generalized epileptiform discharges. We reviewed follow-up EEG study, which were most recent study within 1 year from last visit and compared with clinical outcome, seizure control.

Data from statistical analysis are expressed as medians and interquartile ranges (IQRs) for continuous and ordinal variables, and as counts and percentages for categorical variables. The two groups were compared using the chi-square test or Fisher’s exact tests for categorical and ordinal data, or the Mann-Whitney U test for non-parametric continuous data. A P < 0.05 was considered significant. R Statistics and Microsoft Excel was used for statistical analysis.

3. Ethical statement

This study protocol was approved by the Institutional Review Board of Yangsan Pusan National University Hospital (no. 05-2019-047). The need for informed consent was waived by the board.

Results

1. Demographics

A total of 394 of patients were identified with MISF on EEG between November 1, 2008 and July 31, 2016. Among them, 115 who were diagnosed with epilepsy, treated, and followed up for more than 1 year, and did not meet the exclusion criteria were included in the current study. The patients’ demographic profiles are shown in Table 1. The study population included 68 male patients and 47 female patients (ratio, 1.45:1). The mean onset age was...
4.88 ± 2.99 years, while the median age was 4.5 years (IQR, 2.29 to 6.88). The mean age at MISF on EEG was 8.08 ± 3.53 years, while the median age at MISF on EEG was 6 years (IQR, 5 to 8.67). Seizure type was generalized in 49 (43%) patients and focal in 66 (57%). Of them, 29 patients (25%) had symptomatic epilepsy with lesions on brain MRI. Eight patients (7%) had a history of perinatal problems, 68 (59%) had intellectual disability, 34 (30%) had cerebral palsy, and seven (6%) had genetic disorders (Table 1).

Lesion types revealed through MRI of the brain included periventricular leukomalacia in 11 patients, disorders of neuronal migration (cortical dysplasia, lissencephaly, polymicrogyria, pachygyria, heterotopia) in seven, cerebral vascular disease in five (including one patient with encephalomalacia suspected due to cerebral vascular disease), brain atrophy in two, and others (venous malformation, tubers, dysembryoblastic neuroepithelial tumor, and megalencephalic leukoencephalopathy with subcortical cyst) (Table 2).

The genetic disorders included tuberous sclerosis complex, Prader-Willi syndrome, deletions (deletion of 15q11.2-13.1, 45; XY, del(13, 14)(q10:q10)), 9p trisomy, and Van der Knaap syndrome (megalencephalic leukoencephalopathy with subcortical cyst).

2. Analysis of risk factors that influence therapeutic result

Among the total 115 patients, 84 (73%) were in group A and 31 (27%) were in group B. There was no intergroup difference in sex distribution; both groups showed a male predominance. The mean age at seizure onset was 5.20 ± 2.92 years (median age, 4.88 [IQR, 2.83 to 7.19]) in group A versus 4.01 ± 3.04 years (median age, 2.50 [IQR, 1.79 to 5.79]) in group B, showing no statistical significance (P = 0.005). The mean age at which MISF was first detected on EEG was 8.15 ± 3.22 years (median age, 7.96 [IQR, 6 to 9.67]) in group A versus 7.90 ± 4.33 years (median age, 7 [IQR, 4.88 to 9.5]) in group B, showing no statistical significance (P = 0.773). The clinical factors of family history of epilepsy and febrile convulsion, history of perinatal problems, and gestational age did not differ between groups (Table 3).

A higher proportion of patients in group B had generalized seizures (n = 19 [61%]; P = 0.025). The baseline frequency of seizures at the time of MISF detection on EEG was 4.02 ± 17.52 times/month (median, 0 times/month [IQR, 0 to 0.33]) in group A versus 112.23 ± 357.78 times/month (median, 1 [IQR, 0 to 45]) in group B (P = 0.103). The duration from the first seizure to the start of AED did not differ between the groups (P = 0.656) (Table 4).

Intellectual disability and cerebral palsy, which were suggested related to symptomatic or cryptogenic epilepsy, were more common in group B (P < 0.001 and P = 0.046, respectively). The presence or absence of lesions on MRI did not differ between groups (P = 0.194). Six patients in group A versus one patient in group B had a genetic disorder (no statistically significant difference) (Table 5).

In EEG findings, electrodecrements and abnormal background activities such as diffuse slow waves and poorly organized sleep features were more common in group B (P = 0.005 and P = 0.003, respectively) (Table 6).

3. Clinical course and change in EEG findings with AED therapy

Total follow-up duration of overall patients was 5.8 ± 2.37 years (median, 6.22 [IQR, 3.67 to 8.03]) (Table 7). It was 6.29 ± 2.22 years (median, 7.21 [IQR, 4.89 to 8.17]) in group A versus...
### Table 3. Patients’ clinical profiles according to seizure outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n = 84)</th>
<th>Group B (n = 31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>49 (58.33)</td>
<td>19 (61.29)</td>
<td>0.942</td>
</tr>
<tr>
<td>Female</td>
<td>35 (41.67)</td>
<td>12 (38.71)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at seizure onset</td>
<td>5.20 ± 2.92 (4.8 [2.83–7.19])</td>
<td>4.01 ± 3.04 (2.5 [1.79–5.79])</td>
<td>0.057</td>
</tr>
<tr>
<td>Age at first MISF on EEG</td>
<td>8.15 ± 3.22 (7.96 [6–9.67])</td>
<td>7.90 ± 4.33 (7 [4.88–9.5])</td>
<td>0.740</td>
</tr>
<tr>
<td>Family history of epilepsy</td>
<td>4 (4.76)</td>
<td>2 (6.45)</td>
<td>1.000</td>
</tr>
<tr>
<td>Family history of febrile convulsion</td>
<td>2 (2.38)</td>
<td>1 (3.23)</td>
<td>1.000</td>
</tr>
<tr>
<td>Perinatal problem</td>
<td>6 (7.14)</td>
<td>2 (6.45)</td>
<td>1.000</td>
</tr>
<tr>
<td>Gestational age (yr)</td>
<td>38.79 ± 2.86</td>
<td>37.82 ± 3.64</td>
<td>0.139</td>
</tr>
</tbody>
</table>

Values are presented as number (%), mean±standard deviation (median [interquartile range]), or mean±standard deviation. 
MISF, multiple independent spike foci; EEG, electroencephalography.

### Table 4. Prognostic factors of seizure outcomes associated with seizure profiles

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n = 84)</th>
<th>Group B (n = 31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant seizure type</td>
<td></td>
<td></td>
<td>0.025</td>
</tr>
<tr>
<td>Generalized</td>
<td>30 (35.71)</td>
<td>19 (61.29)</td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>50 (59.52)</td>
<td>10 (32.26)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>4 (4.76)</td>
<td>2 (6.45)</td>
<td></td>
</tr>
<tr>
<td>Seizure frequency at the time of MISF detection (times/mo)</td>
<td>4.02 ± 17.52 (0 [0–0.33])</td>
<td>112.23 ± 357.78 (1 [0–45])</td>
<td>0.103</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>4 (4.76)</td>
<td>3 (9.68)</td>
<td>0.590</td>
</tr>
<tr>
<td>Duration between seizure onset and start of AEDs</td>
<td>0.96 ± 1.55</td>
<td>0.82 ± 1.51</td>
<td>0.656</td>
</tr>
</tbody>
</table>

Values are presented as number (%), mean±standard deviation (median [interquartile range]), or mean±standard deviation. 
MISF, multiple independent spike foci; AED, anti-epileptic drug.

### Table 5. Lesion findings on MRI and comorbidities as prognostic factors of seizure outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n = 84)</th>
<th>Group B (n = 31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology (n = 115)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of lesion on MRI</td>
<td>18 (21.43)</td>
<td>12 (38.7)</td>
<td>0.194</td>
</tr>
<tr>
<td>Comorbidity (n = 115)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intellectual disability</td>
<td>40 (47.62)</td>
<td>28 (90.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>20 (23.81)</td>
<td>14 (45.16)</td>
<td>0.046</td>
</tr>
<tr>
<td>Genetic abnormality</td>
<td>6 (7.14)</td>
<td>1 (3.23)</td>
<td>0.734</td>
</tr>
</tbody>
</table>

Values are presented as number (%). 
MRI, magnetic resonance imaging.

### Table 6. Correlations between electroencephalography findings other than multiple independent spike foci and seizure outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n = 84)</th>
<th>Group B (n = 31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized epileptiform discharge</td>
<td>8 (9.52)</td>
<td>4 (12.90)</td>
<td>0.855</td>
</tr>
<tr>
<td>Electrodecrement</td>
<td>3 (3.57)</td>
<td>7 (22.58)</td>
<td>0.005</td>
</tr>
<tr>
<td>Abnormal background activity</td>
<td>32 (38.10)</td>
<td>22 (70.97)</td>
<td>0.003</td>
</tr>
<tr>
<td>Diffuse slow waves</td>
<td>17 (20.24)</td>
<td>18 (58.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Focal slow waves or asymmetry</td>
<td>3 (3.57)</td>
<td>3 (9.68)</td>
<td>0.404</td>
</tr>
</tbody>
</table>

Values are presented as number (%).
4.48 ± 2.30 years (median, 4.07 [IQR, 2.62 to 6.14]) (Table 7). In group A, they had seizure-free period of 3.87 ± 2.47 years (median, 3.14 [IQR, 2.06 to 5.71]) by last follow-up visit.

A higher number of patients received polytherapy of AED in group A (n = 32 [38.10%]) than in group B (n = 24 [77.42%]) (P = 0.001). The mean number of AEDs used was 1.52 ± 0.91 in group A versus 3.42 ± 1.98 in group B (P < 0.001) (Table 7).

The number of patients treated with anti-seizure therapy other than AED therapy such as a ketogenic diet or vagus nerve stimulation (VNS) was higher in group B than group A (P < 0.001 and P = 0.018) (Table 7).

The findings of follow-up EEG showed improvements in MISF along with improvements in clinical seizure. Among total 109 patients who had follow-up EEG, 81 were in group A and 28 were in group B. More patients in group A (n = 58 [71.6%]) than group B (n = 10 [35.7%]) showed the disappearance of MISF on EEG. Furthermore, EEG findings were normal in more patients in group A (n = 21 [25.9%]) than in group B (n = 0 [0%]) (P = 0.007) (Table 8).

**Discussion**

Very few studies have described the characteristics of patients with MISF since the study of Blume et al. [1,4] in 1970s. The current study aimed to elucidate the clinical characteristics and prognostic factors of patients with post-infantile epilepsy with good prognosis despite the presence of MISF on EEG. For this purpose, this study excluded patients with a history of infantile spasms, a relatively well-known epileptic syndrome with remarkable characteristics and poor prognosis. As a result, we included a considerable number of patients with MISF on EEG who had post-infantile epilepsy and a good response to AED therapy showing improvement in clinical seizures as high as two-thirds (group A, n = 84 [73%]). Patients in the seizure control group required fewer AEDs (1.52 ± 0.91) and were less likely to require adjuvant therapies such as a ketogenic diet and VNS.

In our study, the prognostic factors associated with a poor prognosis and poor seizure control were generalized seizures, premorbid intellectual disability or cerebral palsy, and EEG abnormalities such as electrodecrements and abnormal background activity.

Blume et al. [4] reported that half of their studied patients with MISF had daily and frequent seizures, while one-third had moderate to severe intellectual disability and were difficult to educate. They concluded that these were descriptive characteristics of patients with MISF, while the current study revealed that frequent seizures and intellectual disability were features highly suggestive of a poor prognosis but not characteristics of MISF specifically.

In the literature, the usefulness of EEG is well documented. For example, the EEG abnormality supports the prediction of seizure recurrence in the first unprovoked seizure and the diagnosis of epilepsy [7-9]. In addition to it, our study suggests two aspect of usefulness of EEG. First, abnormal findings additional to MISF are correlated with prognosis. Background abnormalities such as diffuse slow waves or abnormal sleep features were highly suggestive

**Table 7. Differences in the clinical course of post-infantile patients with epilepsy and MISF on EEG**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n = 84)</th>
<th>Group B (n = 31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up duration (yr)</td>
<td>6.29 ± 2.22 (7.21 [4.89–8.17])</td>
<td>4.48 ± 2.30 (4.07 [2.62–6.14])</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Seizure-free duration (yr)</td>
<td>3.87 ± 2.47 (3.14 [2.06–5.71])</td>
<td>-</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Number of AEDs used in treatment</td>
<td>1.52 ± 0.91</td>
<td>3.42 ± 1.98</td>
<td>0.001</td>
</tr>
<tr>
<td>Monotherapy vs. polytherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>52 (61.90)</td>
<td>7 (22.58)</td>
<td>0.018</td>
</tr>
<tr>
<td>Polytherapy</td>
<td>32 (38.10)</td>
<td>24 (77.42)</td>
<td></td>
</tr>
<tr>
<td>VNS</td>
<td>0</td>
<td>3 (9.68)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ketogenic diet</td>
<td>1 (1.19)</td>
<td>9 (29.03)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation (median [interquartile range]), mean±standard deviation, or number (%)

MISF, multiple independent spike foci; EEG, electroencephalography; AED, anti-epileptic drug; VNS, vagus nerve stimulation.

**Table 8. Differences in follow-up EEG findings of post-infantile patients with epilepsy and MISF on EEG**

<table>
<thead>
<tr>
<th>Follow-up EEG findings (n = 109)</th>
<th>Group A (n = 84)</th>
<th>Group B (n = 31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disappearance of MISF</td>
<td>58 (71.6)</td>
<td>10 (35.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Normalization</td>
<td>21 (25.9)</td>
<td>0</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

EEG, electroencephalography; MISF, multiple independent spike foci.
of poor prognosis in seizure control. Second, the improvement on EEG reflected the clinical progression of improvement. Our study showed that normalization or improvement of MISF on follow-up EEG was highly correlated with an improving clinical course. Two-thirds (72.6%) of the seizure control group was accompanied by improvement in MISF on EEG and one-fourth (25.9%) of the seizure control group had fully normalized EEG findings with AED therapy. We suggest that EEG is useful for predicting prognosis of seizure control and estimating clinical improvement with AED therapy.

A recent analysis of MRI lesions and EEG findings in epilepsy patients described that patients with multifocal interictal epileptiform discharges on EEG had a statistically significantly higher rate (68%) of abnormalities on MRI [10]. This was somewhat different from our result that 25% of patients have a lesion on MRI similar to the 21% to 31% of the overall pediatric patients who visited with a first unprovoked seizure [11-14]. In cases of pediatric epilepsy, the rate of abnormalities on brain MRI increased [10]. The reasons that our study findings suggested that the presence of a lesion on MRI was not significantly associated with seizure control might be due to patients with significantly severe lesions being excluded by exclusion criteria of whom diagnosed infantile spasms and early-onset seizures before 1 year of age; thus, a relatively small number of patients with less severe abnormalities on brain MRI were included in our study.

Blume et al. [1] reported that a considerable number of patients with findings of MISF on EEG had generalized seizures. Several studies described that the major seizure type of SE-MISF was brief generalized tonic seizure [5,15-17]. Conversely, in the current study, the percentage of patients with focal seizures was higher than previously reported, while the focal seizure type was a proven good prognostic factor for seizure control. This suggests that seizure type is a major clinical characteristic that influences prognosis.

Since 1992, several studies suggested that epileptic patients with clinical characteristics, especially a severe clinical course and MISF on EEG could be defined as an epileptic syndrome [5,15-18], primarily LGS or SE-MISF, which differs in several ways. In 2006, Yamatogi and Ohtahara [6] defined SE-MISF and summarized its characteristics [6]. SE-MISF is defined as symptomatic generalized epilepsy with age-specific epileptic encephalopathy. They described the characteristics of SE-MISF as: (1) MISF, diffuse slow background activity, and rare diffuse epileptiform discharges on EEG; (2) frequent generalized minor seizures as the main seizure type; (3) mutual transition between the age-dependent epileptic encephalopathies (i.e., Ohtahara syndrome, West syndrome, and LGS); (4) early onset of epilepsy (despite variable SE-MISF onset); (5) association with intellectual disability and neurological abnormality; (6) variable and non-specific etiology; and (7) intractable seizure and psychomotor deterioration.

Likewise, the current study showed that the characteristics associated with a poor prognosis were abnormal background activity on EEG, generalized seizures, and intellectual disability. These are similar to the characteristics of SE-MISF and accounted for three of seven characteristics mentioned by Yamatogi and Ohtahara [6].

Despite SE-MISF not being widely accepted as an epileptic syndrome, efforts to categorize patients with MISF as epileptic syndromes are increasing with our understanding of them. Similarly, our study emphasized that MISF on EEG is not strongly correlated with LGS, SE-MISF, or intractable seizures. Thus, we conclude that MISF should be interpreted correctly and precisely according to individual clinical characteristics, which would prevent errors in the estimation of prognosis during diagnosis and the early phase of treatment.

In current study, seizure control was defined as seizure freedom over 6 months by the last visit. This definition might reflect a short-term outcome in some patients, but in fact the subject had various follow-up periods and seizure-free periods because this study was retrospective. If a prospective study with a long-term follow-up period is conducted, we can further understand the characteristics of benign and severe epileptic patients with MISF and more concise statistics related to the prognosis, such as seizure recurrence, progression of seizure frequency of epileptic encephalopathy, possibility of AED cessation, a long-term seizure-free period, and finally epilepsy cure.

A further study is required to elucidate the clinical significance of MISF in patients with good prognosis, particularly the pathogenesis of epilepsy in cases of idiopathic generalized epilepsy or focal onset seizures.

Conflicts of interest

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

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Author contribution

Conceptualization: JK and SON. Data curation: JK, YJL, AK, YMK, and GMY. Formal analysis: JK and YJL. Methodology: JK and SON. Project administration: JK, YJL, AK, GMY, and SON. Visualization: JK. Writing-original draft: JK. Writing-review & editing: JK and SON.
Acknowledgments

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References


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Introduction

Despite adverse effects on children, poly-substance use during pregnancy continues to be a major public health issue [1]. Psychoactive drugs are toxic to the developing brain, especially during the second and third trimester of pregnancy [2]. Given that insults to the central nervous system have their greatest impact upon cells, circuits and processes that are in accelerated development during the fetal period [3], maternal substance use is strongly associated with short- and long-term negative neurological consequences on the offspring. Short-term effects include abnormal brain growth and organization [4], along with long-term effects that comprise serious cognitive, emotional, behavioral and social problems [5]. Prenatal drug exposure (PDE) is considered a risk factor affecting children's development and thus, it has received considerable attention by researchers in recent years [6-9].

According to averaged data (2012 to 2013) from the National Survey on Drug Use and Health of the United States (NSDUH), about 15.4% of pregnant women ages 15 to 44 had smoked cigarettes, 9.4% used alcohol, and 5.4% used illicit drugs [10]. Like-
wise, between 7% and 11% of European women with substance use problems become pregnant or give birth every year [11]. Although prevalence rates have reached levels of concern, most data are usually obtained with self-reports and thus, substance use in pregnant women might be underestimated due to the stigma and potential legal consequences [3,12-14]. This in turn suggests that more children than those officially reported might have been exposed to drugs in utero.

1. PDE and working memory
PDE effects on cognitive processes have been previously studied [15-19]. For instance, researchers have found a relationship between prenatal tobacco exposure (PTE) and reduced cognitive abilities and academic achievement later in the life [16]. Results from other studies suggest that binge drinking during pregnancy have detrimental effects on children’s cognition [18]. However, fewer studies have specifically examined how PDE affects children’s working memory (WM). WM is broadly defined as the mechanism for retaining a small amount of information in the mind in a temporary state of availability [20]. There are different assessments to measure WM in children for research, clinical and educational purposes including the Digit Span subtest of the Wechsler Intelligence Scale for Children (WISC) [21] and the N-back task [22]. In the Discussion section, we consider issues related to WM measures.

WM has become a major research topic because of its key role on skills and processes required for academic success, which is the main task of children ages 5 through the teenage years [23]. Multiple studies have highlighted the predictive role of WM on academic achievement as well as its relationship with mathematic performance, language comprehension, reading, writing, and problem solving at different developmental stages [24-32]. Taken together, it is reasonable to argue that WM deficits often underlie academic underachievement. However, WM deficits are modifiable and can be identified early, even before academic difficulties become obvious [33]. Ignoring WM deficits might result in deleterious long-term consequences in the child’s health, behavior, and well-being.

2. WM and development
Neuromaging studies have revealed pronounced growth and changes taking place between the ages of 5 and 12 years [34] and much of the WM development occurs after the age of 5 [35]. Cognitive, physical, motor and emotional developmental changes occurring during this period also influence performance on WM assessments. Children usually begin school when they are 5 years old, making it an excellent stage to evaluate WM. With respect to PDE, effects become evident after children begin school when marked increases in cognitive competences are demanded. Therefore, considering the relationship between PDE, WM and children development, we asked the following question in the present study: what are the effects of prenatal exposure to drugs on the WM of children ages 5 to 12? We carried out a systematic review of scientific publications to expand upon existing literature and have a better understanding of the latest research on PDE. Early identification of legal and illicit drugs’ effects on children cognition makes possible to take advantage of the developing brain plasticity to implement interventions aimed at maximizing improvement and preventing future learning problems [36-38].

**Materials and Methods**

1. Study protocol
We used the Joanna Briggs Institute Reviewers’ Manual (JBI-RM) to develop the protocol for this systematic review before conducting the study [39]. The Joanna Briggs Institute is an independent, international organization focused on researching evidence-based healthcare and improving global health. The manual provides detailed guidelines for systematic reviews and meta-analyses. The protocol included the selection of the study designs, population, interventions, comparison groups, measures, search strategy, inclusion/exclusion criteria and critical appraisal (risk of bias assessment). This review includes peer-reviewed journal articles published between 2008 and 2019, in English or Spanish, measuring WM in both male and female children ages 5 to 12 years with a history of prenatal exposure to legal and/or illegal drugs. We narrowed the years of publication (2008 to 2019) to have a precise understanding of the latest research published on this topic.

2. Search strategy
Fig. 1 summarizes our search strategy. We first carried out a limited search in PubMed and PsyCINFO, which are two of the largest databases devoted to peer-reviewed research in biomedicine and behavioral sciences using the following four keywords: prenatal, drugs, exposure, and WM. We analyzed words contained in the titles, abstracts and keywords of the retrieved publications and validated the English and Spanish synonyms of the words for accurate correspondence. Posteriorly, we performed a more inclusive search using an extended set of keywords and their relevant combinations in both English and Spanish: prenatal, fetal, drugs, substances (and specific types such as cocaine, heroin, etc.), exposure, effect, WM, measurement, performance, assessment, and outcome. We searched the following databases: Ebsco Host Research Databases (Academic Search Complete, Fuente Académica, Psychology and Behavioral Sciences Collection, PsyCINFO, Medline), Proquest...
The titles and abstracts of the retrieved articles were carefully reviewed and those that did not clearly meet general criteria were discarded (e.g., animal studies, no outcome of interest). At this point, we applied the detailed inclusion criteria assessment to the articles that had higher possibilities to be included in this review. Studies must have included the following elements: (1) an unexposed group of children as a control; (2) measures of drug use during pregnancy; and (3) control of confounding variables. We contacted the corresponding authors of two publications to request additional information about the measures they used and results obtained in their respective studies. During the analysis, we also reviewed the literature to have detailed descriptions of the WM measures used in those studies. Such information allowed doing a documented decision regarding whether or not the tests or tasks used in those studies were indeed measures of WM.

3. Critical appraisal and data extraction

Our main outcome of interest was studies measuring WM in children who were exposed to psychoactive drugs in utero. Articles that met the inclusion criteria according to the protocol (see Results), were subjected to a rigorous risk of bias assessment completed by the first two authors (critical appraisers). We used the JBI Critical Appraisal Tools approved by the JBI Scientific Committee for systematic reviews, available online (http://joannabriggs.org/research/critical-appraisal-tools.html). We particularly used the checklists for cohort studies and analytical cross sectional studies. Using the JBI-RM, we then extracted relevant information from each article, including the study sample, characteristics and raw data (e.g., weighted mean differences, standard deviations [SDs]) and performed a narrative synthesis by type of drug with the extracted information [39].

Results

We identified 193 publications during the initial search. From that pool, 59 articles were considered as either relevant or of uncertain relevance based on words within the titles and abstracts, and were obtained for full text reading. Out of the 59 studies, we found eight (n = 8) that met our inclusion criteria (Fig. 1): two studies of methamphetamine, three of alcohol, one of tobacco and two of cocaine. After carrying out a critical appraisal on each study to identify possible biases, we found that the eight studies complied with the methodological quality (as quantified separately by each appraiser) and were included in the review. In the next sections, we briefly describe general aspects of each study and report the mean and SD of WM measurements. Table 1 includes other relevant details.

1. Prenatal methamphetamine exposure

Abar et al. [40] analyzed data from the Infant Development, Environment and Lifestyle (IDEAL) longitudinal study on prenatal methamphetamine exposure (PME). Children were engaged in a series of tasks testing executive function and examiners were blind to methamphetamine exposure status. As part of the battery of tests, the authors used the Attention/Concentration index from the Children’s memory scale (CMS), which provides measures of attention and WM [41]. The index mean was 96.33 (SD 14.99) for the PME group and 97.71 (SD 17.56) for the control group, but there were no statistically significant differences in WM (nor executive function) between groups.

Piper et al. [42] carried out a cross-sectional study with children from similar socioeconomic status who were exposed or not to methamphetamine or poly-substances during pregnancy. Children performed a battery of neurobehavioral tests including the Spatial Span subtest of the Wechsler Intelligence Scale for Children IV Integrated (WISC-IV), which offers a measure of visual-spatial WM. In the subtest forward condition, the mean raw score was 5.3 (SD 0.3) for the PME group and 5.7 (SD 0.3) for the unexposed group. In the backward condition, the mean was 4.5 (SD 0.4) for PME
group and 4.9 (SD 0.4) for the unexposed group. There were no statistically significant differences in visual-spatial WM in either condition between groups.

2. Prenatal alcohol exposure
Aragon et al. [43] compared the neuropsychological functioning of children with fetal alcohol spectrum disorders (FASDs) and normal children in the context of a larger epidemiological project. Examiners were blind as to the conditions. Participants completed psychological and developmental evaluations using a battery of tests, including the Italian version of the WISC-R. That scale contains 12 subtests that make up a verbal intelligence quotient (IQ),

### Table 1. Summary of the eight studies reviewed

<table>
<thead>
<tr>
<th>Study</th>
<th>Design/Sample</th>
<th>Measures</th>
<th>Confounder controls</th>
<th>PDE effect on WM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abar et al. (2013) [40]</td>
<td>Longitudinal; n = 320 (PME group, 162; control group, 158); 6.5-year follow-up of children from 4 United States cities (Los Angeles, Des Moines, Tulsa, and Honolulu).</td>
<td>PDE: Maternal self-report or infant meconium immunoassay and gas chromatography–mass spectrometry. WM: Attention/concentration index from the CMS</td>
<td>Neonatal characteristics, maternal age at birth, maternal quantity of self-reported drug use while pregnant and city. Early adversity was included as a mediator of the effect of PME.</td>
<td>No significant differences by exposure condition.</td>
</tr>
<tr>
<td>Piper et al. (2011) [42]</td>
<td>Cross-sectional; n = 66 (methamphetamine/poly-substance exposed group, 31; unexposed group, 35); 7–9-year-old children from Oregon, USA.</td>
<td>PDE: Medical records, maternal questionnaire and urine analysis or maternal legal documentation provided by adoptive parents. WM: Spatial Span test from the WISC-IV-Integrated</td>
<td>ADHD diagnosis and PDE. Unexposed children were recruited from the same community based on similar household income during pregnancy and age as exposed children.</td>
<td>No significant differences by exposure condition.</td>
</tr>
<tr>
<td>Aragon et al. (2008) [43]</td>
<td>Longitudinal; n = 80 (FASD group, 23; control group, 57); 6–7-year-old Italian children.</td>
<td>PDE: Maternal questionnaire. WM: Memory subtest from the WISC-R (Italian translation).</td>
<td>Matched controls were randomly selected from the same first-grade cohort in the same schools. Maternal age, education attainment, and monthly income were similar.</td>
<td>Significant differences by exposure condition. Children diagnosed with FAS or PFAS had lower scores on WM.</td>
</tr>
<tr>
<td>Diwadkar et al. (2013) [44]</td>
<td>Longitudinal; n = 47 (FAS/PFAS group, 17; heavily exposed non-syndromal group, 13; control group, 17); 8.9–10.6-year-old colored children from Cape Town, South Africa.</td>
<td>PDE: Maternal interview WM: Verbal N-back task (letters as stimulus)</td>
<td>Maternal SES, years of education, marital status, age at delivery, parity, and smoking during pregnancy, and child gender, total intracranial volume, age at assessment, IQ, and postnatal lead exposure.</td>
<td>Both groups of exposed children performed poorly than controls on the 2-back task, but the three groups performed well on the 1-back paradigm.</td>
</tr>
<tr>
<td>Quattlebaum et al. (2013) [47]</td>
<td>Cross-sectional; n = 125 (PAE group, 97; non-exposed group, 28); 6–12-year-old children from California, USA.</td>
<td>PDE: Biological mother interview. Among adopted or foster children, medical or legal documentation and witness reports were obtained. WM: Digit Span and Spatial Span subtests of the WISC-III PI</td>
<td>IQ was the sole controlled variable.</td>
<td>WM was significantly different for the PDE group, but only the Spatial Span group differences remained significant after controlling for IQ.</td>
</tr>
<tr>
<td>Bennett et al. (2013) [48]</td>
<td>Longitudinal; n = 18 (PTE group, 7; control group, 11); 12-year-old African American children from Philadelphia, PA, USA.</td>
<td>PDE: Maternal report WM: N-back task (numbers as stimulus)</td>
<td>PDE, neonatal health, environmental risk and sex.</td>
<td>No significant differences by exposure condition.</td>
</tr>
<tr>
<td>Hurt et al. (2009) [49]</td>
<td>Longitudinal; n = 120 (PCE group, 55; control group, 65); primarily 12-year-old African American children.</td>
<td>PDE: Maternal interview, medical records, and maternal and infant urine specimens. WM: Spatial Working Memory and Letter Two-Back</td>
<td>Neonatal characteristics, maternal characteristics at delivery, age at neurocognitive testing, characteristics of the home environment, and current primary caregiver characteristics.</td>
<td>No significant differences by exposure condition.</td>
</tr>
<tr>
<td>Singer et al. (2008) [50]</td>
<td>Longitudinal; n = 371 (PCE group, 192; control group, 179); primarily 9-year-old African American children.</td>
<td>PDE: Maternal report, urine samples and meconium analysis. WM: WM subtests of the WISC-IV</td>
<td>Covariates accounting for demographic, environmental, and medical factors.</td>
<td>No significant differences by exposure condition.</td>
</tr>
</tbody>
</table>

PDE, prenatal drug exposure; WM, working memory; PME, prenatal methamphetamine exposure; CMS, Children’s Memory Scale; WISC, Wechsler Intelligence Scale for Children; ADHD, attention deficit hyperactivity disorder; FASD, fetal alcohol spectrum disorders; PFAS, partial fetal alcohol syndrome; FAS, fetal alcohol syndrome; SES, socioeconomic status; IQ, intelligence quotient; PAE, prenatal alcohol exposure; PTE, prenatal tobacco exposure; PCE, prenatal cocaine exposure.
performance IQ, and full-scale IQ. The memory subtest measures WM and is part of the verbal IQ. In that subtest, the mean was 8.13 (SD 3.42) for the FASD group and 10.23 (SD 3.10) for the control group, but there were no statistically significant differences between groups. When comparing the two groups on the verbal, performance, and full scale mean IQ scores from the WISC-R, the FASD group showed significantly lower scores on verbal IQ, performance IQ, and full-scale IQ.

Diwadkar et al. [44] used the n-back task and functional magnetic resonance imaging (fMRI) to measure and compare WM in three groups: children with full fetal alcohol syndrome (FAS) or partial fetal alcohol syndrome (PFAS); children heavily exposed to alcohol (HE) without FAS or PFAS; and control children. The examiners were blind with regard to maternal alcohol consumption history and children diagnosis. The principal n-back task outcome was d-prime, which measures the “number of correct button presses, adjusted for false alarms, to correct for any tendency to press the same button regardless of whether the stimulus was seen previously” [44]. They measured WM inside and outside of the MRI scanner.

For the 1-back task outside the scanner, the d-prime mean was 2.41 (SD 0.78) for the FAS/PFAS group, 2.12 (SD 0.75) for the HE group and 2.25 (SD 1.01) for the control group. For the 1-back task inside the scanner, the d-prime mean was 2.14 (SD 0.81) for the FAS/PFAS group, 2.12 (SD 0.80) for the HE group and 2.26 (SD 0.81) for the control group. There were no statistically significant differences in the 1-back task between groups either outside or inside the MRI scanner. For the 2-back task outside the scanner, the d-prime mean was 1.13 (SD 0.67) for the FAS/PFAS group, 0.99 (SD 0.47) for the HE group and 1.39 (SD 0.72) for the control group. Again, there were no statistically significant differences in the 2-back task between groups. fMRI data indicated that the three groups recruited different elements of the cortico-striatal-cerebellar network, which is known to be involved in WM [45,46]. In terms of IQ assessment, all the children were administered the Wechsler Intelligence Scale for Children, fourth edition (WISC-IV). The WISC-IV measures intellectual ability of children from 6 to 16 years and provides an overall measure of general cognitive ability. It also measures intellectual functioning in verbal comprehension, perceptual reasoning, WM, and processing speed. The IQ scores of the children in the FAS/PFAS group were lower than the controls and tended to be lower than those in the HE group.

Quattlebaum and O’Connor [47] carried out a comprehensive, multi-informant assessment of neurocognitive, emotional, social, behavioral, and adaptive functioning in children with FASD, which included the Wechsler Intelligence Scale for Children-III as a Process Instruments (WISC-III PI). The WISC-III PI contains 19 subtests and complements the WISC-III by allowing to identify which process is deficient when the examinees perform poorly in the latter. They measured WM using the Digit Span and Spatial Span subtests of the WISC-III PI. In the Digit Span task, means were 8.68 (SD 3.07) for the prenatal alcohol exposure (PAE) group and 10.14 (SD 2.72) for the control group, and in the Spatial Span task, means were 8.35 (SD 3.57) for the PAE group and 11.61 (SD 3.14) for the control group. Both subtests produced a statistically significant overall effect after controlling for IQ, although the individual effect of the Digit Span subtest was not statistically significant. The IQ was assessed with the Kaufman Brief Intelligence Test, a brief individually administered measure of verbal and non-verbal intelligence.

3. Prenatal tobacco exposure

Bennett et al. [48] used an event-related fMRI design to measure brain activity and WM using the n-back task in a sub-sample of a longitudinal PDE study. The mean of omission errors in the n-back task was 11.4 (SD 7.1) for PTE group and 8.1 (SD 4.9) for controls, and the mean of commission errors was 2.7 (SD 2.0) for PTE and 4.9 (SD 5.0) for controls. However, there were no statistically significant differences in the n-back task performance between groups. In terms of neuroimaging, the authors found statistically significant differences in whole brain activation between PTE children and controls during correct responses. The PTE group showed greater activation of inferior parietal regions, whereas control children showed greater activation of bilateral inferior frontal regions during the WM task.

4. Prenatal cocaine exposure

The neurocognitive study of Hurt et al. [49] was designed to assess the effects of prenatal cocaine exposure (PCE) on different domains. They measured WM using the spatial WM task and the Letter Two-Back task. In the spatial WM task, the mean error score was 48.8 ± 15.4 for PCE and 46.7 ± 17.3 for controls and the standard score was 93.4 ± 9.2 for PCE and 93.4 ± 11.3 for controls. In the Letter Two-Back task, the mean total correct score was 108.5 ± 5.8 for PCE and 108.1 ± 6.1 for controls. Authors stated that the WM scores were in the average range, with all scores falling below the mean for the standardization sample. They found no statistically significant differences between groups and no evidence of WM impairment caused by PCE after controlling for multiple confounding child and environmental variables.

Singer et al. [50] conducted a cognitive and school achievement assessment as part of a longitudinal study. The study examiners were unaware of the children’s cocaine exposure status. They measured WM using the WISC-IV. The mean WM IQ was 88.56 (SD
14.20) for the PCE group and 89.84 (SD 16.28) for the unexposed group. They found no statistically significant differences between groups, although discrete effects of alcohol exposure were discernible on WM IQ.

**Discussion**

The aim of this study was to review the effect of PDE on children’s WM in light of published literature regarding the negative consequences of poly-substance use during pregnancy. Specifically, this systematic review included eight studies measuring WM in children prenatally exposed to methamphetamine, alcohol, tobacco, or cocaine. We discuss relevant findings, inconsistencies between studies and limitations of this systematic review.

1. **Methamphetamine and WM**

Although no significant effects of PME in children’s WM were found in the two studies reviewed [40,42], results were possibly affected by distinct limitations. For example, Piper et al. [42] used a small sample and did not control for the effect of attention deficit hyperactivity disorder pharmacotherapy, which is known to enhance cognitive performance [51,52]. Nonetheless, both studies reported important findings about executive functions. Abar et al. [40] pointed that although they did not observe direct effects of PME on executive function deficits, there was an indirect effect through early adversity. According to Piper et al. [42], the neurobehavioral assessments revealed pronounced executive dysfunction and a slight reduction in spatial memory. Based on those observations, interventions for neurobehavioral remediation in children prenatally exposed to drugs were suggested. Currently, PME studies in general [8], and their possible effects on children’s WM in particular are scarce and thus, the available information is not enough to establish clear conclusions about the interaction between PME and WM in children.

2. **Alcohol and WM**

All three studies reviewed here found negative effects of PAE on children’s WM. Results were expected because it had been established that PAE produces a variety of effects in the offspring [53] and is a leading preventable cause of birth defects and developmental disabilities [54-56]. Nonetheless, it is important to highlight the history of PAE in those studies. The estimated number of drinks consumed on a typical day during pregnancy was 0.47 (0.71) for the FASD group and 0.30 (0.49) for the control group in the study of Aragon et al. [43]. The women in the two alcohol consuming groups (FAS/PFAS and HE) in the study of Diwadkar et al. [44] concentrated their drinking on 1.2 to 1.4 days/week on average and women in both groups met criteria for the revised National Institute on Alcohol Abuse and Alcoholism (United States) criterion for binge drinking by women (four or more drinks/occasion). In the study of Quattlebaum and O’Connor [47], a comprehensive history of PAE was obtained by means of the health interview for women. Among adopted or foster children, medical and legal record documentation, as well as reliable witness reports of PAE, were obtained. Children with unknown exposure were not included in the study. Researchers took rigorously steps to obtain reliable data about PAE. The fact that exposed participants meet diagnostic criteria for FASD according to dysmorphological examination suggest that the informed PAE might be underestimated.

The FASD has been used to emphasize the continuum nature of these effects [57] and the evidence from multiple studies demonstrate why alcohol remains the most widely studied prenatal drug of abuse [4]. One important contribution of studies analyzed here is that alcohol not only negatively affects physical characteristics (e.g., facial morphology, body size), but it also affects the development of specific neurocognitive processes such as WM [57]. Indeed, there is evidence that PDE in general may be a risk factor for specific deficits, rather than global deficit [58]. Hence, it may be useful to examine particular aspects of neurocognitive functioning which might be more sensitive to PDE than global assessments.

3. **Tobacco and WM**

Bennett et al. [48] did not find significant differences in WM between children prenatally exposed to tobacco and controls, but the result could be related to the small sample size (n = 18) and measure used (n-back task). Researchers have criticized the use of the n-back task as a WM measure (see discussion below). In spite of this limitation, fMRI data revealed differences in brain activity during WM task between comparison groups [48], suggesting that WM examination in children prenatally exposed to tobacco using exclusively a neuropsychological assessment might be insufficient to detect differences between groups. A better approach is to combine neuropsychological assessment with neuroimaging techniques whenever possible.

4. **Cocaine and WM**

Hurt et al. [49] and Singer et al. [50] did not find significant effects of PCE on children’s WM. Although the sample sizes of the studies were relatively large, they included several measures of PDE and also controlled confounding variables, the results were not generalizable because children were primarily African Americans. Findings of both studies showed that PCE is not a potent risk factor affecting children’s cognitive development and stressed out the importance of identifying postnatal environmental factors to explain...
the performance [49]. In addition, their findings are consistent with a comprehensive review [6] that examined the effects of PCE on growth, cognitive ability, academic functioning and brain structure and function among school-aged children. After controlling for environmental factors, only PCE effects were reliably reported in sustained attention and behavioral self-regulation [6].

5. Concerns regarding PDE research
Relevant issues related to study designs, control of confounding variables and measures used in PDE research in general and WM research in particular are briefly discussed next.

1) Study designs
Limitations regarding the inclusion and exclusion criteria represent one issue. For instance, studies often exclude participants with physical, psychiatric, or developmental disabilities and therefore, findings might not be sustained in samples with these particular conditions. Another concern are the sample sizes because some studies have used small samples for justified reasons (e.g., budget, technical support) although larger samples have more power to detect differences between groups.

2) Control of confounding variables
Controversial findings in PDE research might relate to inadequate attention of potential confounders. For instance, the mothers of children prenatally exposed to drugs are frequently poly-substance users and consequently, multiple drug interactions might underlie the deficits observed. Researchers should analyze the results with discretion, avoiding the attribution of effects exclusively to one drug, as samples with single drug exposures are difficult to find and would not be relevant to the populations under study [59]. In addition to differences in PDE (e.g., type of drug, frequency) postnatal factors such as SES, caregiver psychopathology and violence experiences might influence the results. Factors contributing to childhood disability include caretakers’ characteristics and behaviors, inadequate housing, crowding, deviant peer and adult models, poorly educated adult models, inadequate health care access and minority status [3]. Hence, it becomes necessary to consider sociodemographic, medical and environmental factors in PDE research.

3) Measures
Another important issue in PDE research relates to reliable drug exposure measures [60]. The prevailing methods to detect PDE are maternal self-reports and urine toxicology screens. Although self-reports are cost-effective methods to assess time and amount of drug use during pregnancy, the veracity and recall accuracy could be questioned in studies relying exclusively on self-reports [4]. Given that precise information of drug exposure is difficult to recall and might be affected by the stigma of admitting drug use during pregnancy, drug use during this period is often non-disclosed. On the other hand, urine toxicology screens allow the detection of several drugs, but they only detect recent use, provide no information about frequency and quantity, and could underreport exposure given drugs’ detection span [61-63]. Koninjenberg [60] proposes the use of maternal self-reports and laboratory tests in PDE studies.

Using particular assessment instruments might be also problematic if they are not suitable for examining the outcome of interest. For example, it could be the use of instruments translated to the language of the population to be studied without psychometric properties for that population. An Afrikaans translation of the WISC-IV was used in the study of Diwadkar et al. [44]. Moreover, the use of measurement instruments for which the psychometric properties have not been examined or the empirical evidence does not support their use, represents an ethical issue. Results and interpretations from instruments without adequate psychometric properties must be taken with discretion.

4) Measures of WM
WM research has been complicated by the various definitions of WM itself and theoretical framework assumed, yielding different methods of assessment [64]. Researchers must use measures with sufficient sensitivity to detect WM deficits in children. Such process implies analyzing each task to ensure that cognitive (e.g., sustain attention, speed processing) and non-cognitive (e.g., computer or communication skills) demands are similar among them.

Another problem relates to how task performance is measured. From a research perspective, computerized cognitive tasks comprise standardized administration and data gathering from a large numbers of trials, including reaction time measures [65], but participants’ computer abilities could affect the results [64]. Computerized tasks might also be less sensitive than manual tasks for measuring executive function deficits in specific clinical groups and they might have poor ecological validity [65].

The distinction between simple and complex span tasks reflects the difficult context regarding the assessment of WM. Simple span tasks require to immediately recall short lists of stimulus while complex span tasks involve both storage and control processes that maintain the information accessible in the service of higher-order cognition [66]. When translating this into PDE research, perhaps simple tasks might not discriminate between children prenatally exposed to drugs and non-exposed children. It seems that complex tasks might be most sensitive to behavioral performance differenc-
es among children prenatally exposed to drugs [43].

The classification of a WM measure as either simple or complex should be derived not only from theoretical analyses, but also from empirical data. Two frequently used measures to assess WM, the Digit Span subtest from the WISC and the n-back tasks, could illustrate this issue. The Digit Span subtest is a recall measure of numerical sequences of increasing difficulty. It comprises a forward condition (simple task) and a backward condition (complex task). Even though it can be regarded as a WM measure, the performance may be influenced by other factors such as attention and comprehension [43]. N-back tasks are continuous-recognition measures that present sequences of stimulus and the participant decides whether it matches the one appeared n items ago. N-back has face validity as a WM task because participants must rehearse and update sequence while responding to each item. However, in contrast to WM spans, empirical validation of the n-back task as a WM measure are limited [67]. In one of the few published studies [66], researchers found that the n-back and WM span were weakly correlated, suggesting that they do not reflect a single construct. Authors stated that the results of their study provide little evidence of n-back’s validity as a WM task measuring the same executive processes involved in complex span. Retrieval demands between the complex span and the n-back are different because the first one demands serial recall, while the latter demands recognition. Recall tasks more realistically reflects the complex cognitive behavior exhibited in reading, reasoning and problem solving because all require the rapid recall of recently acquired knowledge [68]. In addition, despite its widespread use in neuroimaging studies, investigation of the n-back as a clinical measure is scarce [69]. Its clinical utility to predict cognitive ability is not clear, but the n-back task is useful in WM research because it allows load to be manipulated in a simple way [67].

Research that incorporates more than one type of data would enhance the results. For example, fMRI is a non-invasively method to assess brain activity during cognitive, perceptual or motor tasks [48,70] and it has been used in PDE studies to detect differences in brain activity even when neuropsychological or behavioral outcomes appear unaffected. Brain imaging might reveal differences in neural activity during task performance and thus, it is recommended to focus on qualitative and quantitative data at both the behavioral and neural level.

6. Conclusion

The limited number of studies discussed in this systematic review did not allow us to establish conclusions about the effects of PDE on children’s WM. However, it is clear that alcohol exposure in utero continues to be a major public health concern. Based on the studies reviewed here, PAE seems to negatively affect children’s WM. In addition, one relevant methodological constrain we found relates to the variety of instruments and tools (e.g., psychological testing, computerized tasks) used to measure WM. Multiple ways of measuring WM might affect the results and consequently, the conclusions reached. Although inconsistencies in the results of studies exploring PDE and WM may be associated with these and perhaps other methodological issues, they represent together a major challenge for neurology, neuropsychology and cognitive sciences in general. Well-designed studies to obtain more precise information about the effects of PDE in children’s WM are strongly recommended.

7. Limitations

The present systematic review has several limitations that should be addressed. First, our study was limited to electronic publication search, occluding publications in printed journals that perhaps complied with the inclusion criteria. However, we supplemented the electronic search with a revision of references cited in the articles to identify other relevant studies and compensate partially for this limitation. A second constraint was the participants’ age range (5 to 12 years old). As mentioned before, this systematic review focused on this particular age range because school endeavors demand complex cognitive competences during this life period. Such demands could evidence the effects of PDE that would be difficult to identify and intervene at an early age or in other settings. A third limitation is the year of publication (2008 to 2019). We selected those specific years to include recent findings on this topic and therefore, previous studies were excluded. In spite of these limitations, this systematic review provides relevant implications for future research exploring specific causal relationships between PDE and WM.

Conflicts of interest

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

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Formal analysis: SLH and NDCB. Funding acquisition: NDCB.
Methodology: NDCB, and GB. Project administration: SLH and NDCB. Visualization: SLH and NDCB. Writing-original draft: SLH. Writing-review & editing: SLH, NDCB, and GB.

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Voltage-gated sodium channels are composed of one pore-forming α subunit and one or two auxiliary β subunits. So far, nine voltage-gated sodium channel α-subunits (Na\textsubscript{V}1.1–Na\textsubscript{V}1.9) have been identified [1]. Among them, Na\textsubscript{V}1.6 is encoded by the SCN8A gene, and widely expressed in the projection neurons of the cerebral cortex, hippocampus, and cerebellum [2]. In general, pathogenic variants (PVs) in SCN8A associated with early onset epileptic encephalopathy are de novo missense variants, and electrophysiological studies of such PVs typically reveal ‘gain of function’ leading to enhanced sodium current [3]. Since the first report of SCN8A-related epilepsy in 2012, more than 100 cases have been reported. SCN8A PVs mostly causes early onset epileptic encephalopathy type 13, which presents with infantile onset epilepsy accompanied with developmental delay and cognitive impairment [1]. However, recent reports have demonstrated that missense PVs in SCN8A present with mild phenotypes [1,2,4].

A 6-month-old male infant was admitted to the emergency department at Ulsan University Hospital due to seizure. Until the day before admission, the infant was healthy with no history of medication, head trauma, or recent immunization. Upon arrival at the emergency department, the patient’s seizure had already ceased. His body temperature was 37.1°C; heart rate was 158 beats/min; and respiratory rate was 26 breaths/min. His pupils were isocoric, and the light reflex of both eyes was prompt. One hour after arrival at the emergency department, another generalized tonic-clonic seizure developed, and it subsided soon after intramuscular administration of lorazepam. The patient was born at 40 weeks’ gestation via a cesarean section without complications. His growth and development was age appropriate. The patient’s parents had no history of neurological diseases, including epilepsy. He had no siblings. Laboratory results revealed that sodium was 136 mmol/L, total calcium 11.1 mg/dL, and glucose 99 mg/dL. Electroencephalography revealed normal finding. Magnetic resonance imaging of the brain showed no abnormalities except a small developmental venous anomaly in right frontal lobe. On day 1, the patient showed a third generalized tonic-clonic seizure in the pediatric ward, and it was managed with intravenous phenobarbital. He had no additional seizure afterward, and was discharged on day 4. After discharge, the patient maintained oral phenobarbital administration (5 mg/kg/day) without further seizure for 2 months. However, at the time of a phenobarbital taper, the patient developed two additional generalized seizures lasting about 1 minute within 3 hours, and...
was readmitted to the emergency department. During the second hospitalization, he had 10 additional seizures, all of which were generalized tonic-clonic seizures lasting between 15 seconds and 15 minutes. Intravenous valproate and levetiracetam, and oral clobazam failed to control the seizures. The patient’s seizures were eventually controlled with commencement of oxcarbazepine administration on day 15. He was discharged on day 21 with discharge medications of oxcarbazepine, valproate, and clobazam. For molecular diagnosis, we performed targeted gene sequencing of 118 epilepsy-related gene panel at GC genome (Yongin, Korea), which revealed two missense variants in SCN8A (NM_014191.3:c.5630A>G; p.Asn1877Ser) and CHRNB2 (NM_000748.2:c.691C>T; p.Arg231Cys). The SCN8A variant has not been observed in the population databases, but has previously been reported in patients with epilepsy (PMID: 27210545, 27875746, 29100083, 27864847, 28923014, 31487502, 31164858, 30851583, 30776697). On the other hand, the population frequency of the CHRNB2 variant was estimated to be 0.0028% in the population database (gnomAD; https://gnomad.broadinstitute.org/), but has not been reported in patients with epilepsy. By Sanger sequencing of the SCN8A and CHRNB2 variants in the patient and his parents, the SCN8A variant was not observed in both parents while the CHRNB2 variant was observed in his father confirming de novo occurrence of the SCN8A variant (Fig. 1). Although the CHRNB2 gene is known to be associated with autosomal dominant nocturnal frontal lobe epilepsy, the patient’s father never had a seizure in his life and had no neuro-

![Next-generation sequencing (NGS)](image1.png)

![Sanger sequencing](image2.png)

**Fig. 1.** Identification of de novo SCN8A variant. (A) Next-generation sequencing of the patient revealed a heterozygous variant in the SCN8A gene (NM_014191.3:c.5630A>G; p.Asn1877Ser). (B) Sanger sequencing of the patient and both parents confirmed the de novo occurrence of the SCN8A variant.
### Table 1. Clinical features in four cases of the SCN8A c.5630A>G (p.Asn1877Ser) variant presenting with a mild phenotype

<table>
<thead>
<tr>
<th>Study</th>
<th>Pt.</th>
<th>Age/sex</th>
<th>Seizure onset</th>
<th>Seizure type</th>
<th>Motor development</th>
<th>Cognitive outcome</th>
<th>EEG</th>
<th>MRI</th>
<th>Respond to AEDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anand et al. (2016, UK) [4]</td>
<td>1</td>
<td>16 mo/M</td>
<td>5 mo</td>
<td>Focal seizure followed by generalization</td>
<td>Normal (head control at 3 mo; sit independently at 6 mo; walk and climb stairs at 16 mo)</td>
<td>Normal (babble, say a few words at 16 mo)</td>
<td>Normal (5 mo); slow, disorganized background rhythm for age (8 mo)</td>
<td>Normal (5 mo)</td>
<td>(+) PHT, CBZ, (-) not effective</td>
</tr>
<tr>
<td>Wang et al. (2017, China) [1]</td>
<td>2*</td>
<td>42 yr/M</td>
<td>4 mo</td>
<td>GTC</td>
<td>Normal (head control at 2 mo; sit independently at 9 mo)</td>
<td>Unavailable</td>
<td>Spikes in right frontal; 3–4 Hz slow waves in occipital region (8 mo)</td>
<td>Normal (7 mo)</td>
<td>(+) PHT, VPA, (-) LEV, VPA</td>
</tr>
<tr>
<td>Present study</td>
<td>3</td>
<td>1 yr/F</td>
<td>5 mo</td>
<td>GTC</td>
<td>Normal (head control at 3 mo; sit independently at 8 mo; walk unaided at 14 mo)</td>
<td>Normal (say “Mama” and “Papa” at 13 mo)</td>
<td>Normal (6 mo, 8 mo)</td>
<td>Normal (6 mo)</td>
<td>(+) OXC, (-) LEV, CLB</td>
</tr>
<tr>
<td>Present study</td>
<td>4</td>
<td>14 mo/M</td>
<td>6 mo</td>
<td>GTC</td>
<td>Normal (head control at 3 mo; sit independently at 8 mo; walk unaided at 14 mo)</td>
<td>Normal (say “Mama” and “Papa” at 13 mo)</td>
<td>Normal (6 mo, 8 mo)</td>
<td>Normal (6 mo)</td>
<td>(+) OXC, VPA, PB</td>
</tr>
</tbody>
</table>

Pt, patient; EEG, electroencephalography; MRI, magnetic resonance imaging; AED, anti-epileptic drug; PHT, phenytoin; CBZ, carbamazepine; GTC, generalized tonic-clonic seizure; VPA, valproate; LEV, levetiracetam; OXC, oxcarbazepine; CLB, clobazam; PB, phenobarbital.

*Patient 2 is the father of Patient 1.

In general, seizures caused by SCN8A PVs begin in infancy, particularly within 6 months of age. Although focal seizures are the most common, diverse seizure types, including epileptic spasms, atypical absence, myoclonic, and generalized tonic-clonic, can present. Seizures in patients with SCN8A PVs are often controlled effectively by sodium channel blockers, such as phenytoin, carbamazepine, and oxcarbazepine, although other anti-epileptic drugs fail to control seizures [3]. Although infants with SCN8A PVs show normal or mildly delayed development prior to seizure onset, the majority of patients have apparent developmental delay or regression after seizure onset. Motor manifestations, such as hypotonia, dystonia, hyperreflexia, and ataxia can also be presented [3].

Recently, however, Gardella et al. [2] reported that 16 individuals in 3 families with the same missense variant (c.4447G>A, p. Glu1483Lys) in SCN8A gene presented with benign infantile seizures and paroxysmal dyskinesia.

To the best of our knowledge, so far four cases with SCN8A c.5630A>G (p.Asn1877Ser) variant presenting with a mild phenotype, including the present case, were documented (Table 1) [1,4]. However, the same variant presenting with a more severe phenotype of epilepsy and intellectual disability has been also reported [5]. The SCN8A c.5630A>G (p.Asn1877Ser) is located at the proximal 2/3 of the c-terminal domain of Na1.6 [4]. This is a highly conserved part of the Nav1.6 protein which contains binding sites for interacting proteins. One report speculated that protective genetic variants, or modifier genes which diminish the severity of the SCN8A, could result in a milder phenotype [4].

This case demonstrated that SCN8A c.5630A>G (p.Asn1877Ser) variant can present with relatively mild neurological manifestations. Early genetic testing in patients with refractory seizures with unknown etiology is critical, since identification of epilepsy related to specific gene mutations may help determine the most effective medication, such as sodium channel blockers for SCN8A-related epilepsy, and predict the prognosis.

This study was approved by the Institutional Review Board of Ulsan University Hospital (IRB No. 2020-03-011). Informed consent was waived by the board.

### Conflicts of interest

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

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Conceptualization: KYL. Data curation: EK, CSK, SP, and KYL. Formal analysis: CSK and KYL. Methodology: CSK, SP, and KYL. Visualization: CSK. Writing-original draft: EK and KYL. Writing-review & editing: CSK and KYL.

References


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Salmonella encephalopathy is an infrequently reported septic encephalopathy characterized by gastrointestinal manifestations (including fever, vomiting, diarrhea, and abdominal pain), due to non-typhoidal Salmonella infection. It is often accompanied by altered consciousness, seizures, or other neurologic symptoms. The pathophysiology of septic encephalopathy has not yet been well established; however, some recent reports reveal that the levels of cytokines, such as interferon gamma, tumor necrosis factor-alpha, and interleukins 6, 8, and 10, in blood and the central nervous system (CNS) are elevated in patients diagnosed with this disease [1]. Several intravenous antibiotics have been used for the empirical treatment of patients suspected of having Salmonella encephalopathy, but these have not enabled successful and complete recovery. Ichikawa et al. [1] reported that high-dose methylprednisolone could be used for treating patients with Salmonella encephalopathy, without any systemic and neurologic sequelae. We encountered a case of a 15-year-old boy diagnosed with Salmonella encephalopathy, who was successfully treated using intravenous immunoglobulin (IVIG) and dexamethasone in addition to empirical antibiotics.

Written informed consent by the patients was waived due to a retrospective nature of our study. A 15-year-old boy who had been previously healthy visited the emergency department with a 5-day history of fever, and a 3-day history of periumbilical pain, vomiting, diarrhea, and headache. He had eaten soy sauce-marinated fresh crabs continuously for 2 weeks before hospitalization. During those 2 weeks, he sometimes presented abdominal pain, nausea, and diarrhea those were wax and wane. Since 5 days before hospitalization, his symptoms had aggravated gradually. After 13 hours of hospitalization, he developed confusion, drowsiness, generalized tonic seizures, and psychiatric symptoms such as a change in character and inappropriate verbal communication. His body temperature was 39.1°C, blood pressure was 127/58 mm Hg, heart rate was 110/min, and respiratory rate was 20/min. A physical examination revealed a mildly distended abdomen and periumbilical direct tenderness without rebound tenderness. The initial neurologic examination, revealed isochoric pupils with a normal light reflex, full extraocular movement in both eyes, normal motor/sensory function, normal deep tendon reflex, and positive meningeal irritation sign, including neck stiffness, Brudzinski’s and Kernig sign. His laboratory findings were as follows: white blood cell (WBC) count, 15,600/μL; hemoglobin, 15.3 g/dL; platelet count, 296,000/μL; C-reactive protein level, 2.15 mg/dL; erythrocyte sedimenta-
tion rate, 58 mm/hr; high-sensitivity troponin-I level, 732 pg/mL; and N-terminal prohormone brain natriuretic peptide (NT-proBNP) level, 928 mg/dL. The results of cerebrospinal fluid (CSF) analysis were as follows: WBC, 405/μL (polymorphonuclear leukocytes, 17%; mononuclear cells, 83%); red blood cell count, 49/μL; adjusted WBC, 404/μL; glucose level, 48 mg/dL; and total protein concentration, 184 mg/dL. His serum glucose was 101 and CSF/serum glucose ratio was 0.47. Polymerase chain reaction (PCR) analyses were conducted to exclude CSF enterovirus, herpes simplex virus types 1, and 2, and a few bacteria including Streptococcus pneumoniae, Haemophilus influenzae type B, Neisseria meningitidis, Group B Streptococcus, and Listeria monocytogenes. PCR results in CSF are all negative. Bacterial culture tests using the CSF, blood, and stool also yielded negative results. PCR analysis of his stool showed a positive reaction only for Salmonella spp., but not for Shigella, Vibrio, Campylobacter, Escherichia coli, Clostridium, and Yersinia. Brain magnetic resonance imaging (MRI) with diffusion-weighted imaging was taken on the second day after the encephalopathic symptoms began. MRI revealed no abnormal signal in the gray and white matter (Fig. 1). However, overnight video-electroencephalography, revealed diffuse background slow waves with only few focal epileptiform discharges without subclinical/clinical seizures and those were normalized on next day. Electrocardiography revealed a normal sinus rhythm (Fig. 2). Echocardiography was performed because of the high levels of NT-proBNP and troponin-I in the laboratory examinations, and it revealed mild coronary ectasia of the left anterior descending artery (4.9 mm; Z-score, 3.2). Other findings, including the ejection fraction,
Salmonella encephalopathy is a rarely reported disease, which is considered a manifestation of nontyphoidal Salmonella enteritis [1]. Arii et al. [2] recommended the diagnostic criteria for Salmonella encephalopathy as follows: (1) encephalopathic features, defined as the presence of an altered state of consciousness, altered cognition or personality, or seizures; (2) detection of nontyphoidal Salmonella spp. in stool; (3) absence of other viral or bacterial infection associated with CNS abnormalities; and (4) absence of an alternative explanation for the neurologic or systemic disease [2]. In our patient, the result of the CSF bacterial culture test was negative; however, pleocytosis (WBC, 405/μL) and increased protein concentration (184 mg/dL) were noted in the CSF. The findings were highly suspicious of the possibility of bacterial encephalitis. Moreover, the results of the PCR analyses using CSF, stool, and respiratory tract specimens were all negative except Salmonella spp. from the stool. The extraneural infection of Salmonella without isolation of any viruses or bacteria in the CSF and the systemic manifestations such as cardiac involvement were suggestive that the neurogenic symptoms were systemic manifestation, so called septic encephalopathy due to increased levels of several cytokines or endotoxins [3]. Although we did not examine inflammatory mediators, some reports have shown that cytokines or endotoxins may play important roles in Salmonella encephalopathy [1]. Regarding prognosis, Salmonella encephalopathy shows severe neurologic sequelae in most diagnosed patients [2]. However, Ichikawa et al. [1] showed favorable outcomes with high-dose methylprednisolone pulse (30 mg/kg/day for 3 days) and empirical antibiotics. IVIG and steroids are used to treat various immune-mediated disease, including febrile infection-related epilepsy syndrome and autoimmune encephalitis [4,5]. In clinical settings, however, the decision to use IVIG is often delayed because of delayed diagnosis, which could limit its benefits [5]. We used intravenous dexamethasone and IVIG from treatment initiation. We concluded that the early use of both intravenous dexamethasone and IVIG was helpful in the treatment of Salmonella encephalopathy.

Conflicts of interest

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

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References

The sinus headache is a widely accepted diagnosis among patients and primary-care physicians. Contrary to general belief, the cases that fulfilled the International Headaches Society (IHS) criteria for "headache attributed to acute rhinosinusitis" is uncommon [1]. Sinus involvement has not been proven in up to 90% of self- or health-care provider-diagnosed sinus headaches, which often satisfy the IHS criteria for migraine [1]. Furthermore, sinus headaches are generally self-limiting [2]. Based on these findings, the relevance of sinus headache has declined steadily in the medical community [2]. However, headache caused by sphenoid sinusitis is a different matter. Sphenoid sinusitis may be a potentially serious disorder, which typically affects preadolescent and adolescent patients and may cause loss of vision, permanent multiple cranio-pathies, and intracranial spread [3]. Most patients with sphenoid sinusitis present with headache; however, the symptoms are variable [3]. Physical examination, such as palpation of the face, is generally not useful for the detection of sphenoid sinus pathology due to its anatomical location [3]. Therefore, unless pediatric neurologists have a high suspicion of sphenoid sinusitis as the cause of a headache, treatment can be delayed with potentially fatal consequences. Here, we report the case of an adolescent male with severe headache and intractable facial pain that was resistant to medical treatment who recovered immediately after surgical management of sphenoid sinusitis.

A 12-year-old male visited the emergency room with a 7-day history of progressive headache and fever that developed an hour before arrival. On initial assessment, his body temperature was 38.4°C, the white blood cell count was 11,210/mm³, and his C-reactive protein (CRP) level was 2.8 mg/L (normal limit, 0 to 5). His neurological examination was unremarkable, including no signs of meningeal irritation and normal cerebrospinal fluid examination. He complained severe throbbing headache in the right temporal and occipital regions, sensitivity to light, and nausea. He had no history of the previous headache. Facial tenderness or pain, and post-nasal drip were not observed. The headache was aggravated by not only physical activity but also lying down. Magnetic resonance imaging (MRI) revealed opacity of the right ethmoid sinus, left maxillary sinus, and bilateral sphenoid sinus, but was otherwise normal (Fig. 1). The patient was treated with ampicillin/sulbactam and ketorolac based on the possibility of status migrainosus with acute bacterial infection of the paranasal sinuses. However, after admission, his clinical course progressed rapidly: fever persisted up to 40°C, his CRP levels increased to 50 mg/
dL, and the severity of the headache intensified in the right tempo-
ral region of his head. On day 3 of admission, the patient appeared
septic and complained of pain in the right retro-orbital region and
face. Because the aching facial pain was consistent with the distri-
bution of the trigeminal nerve, we strongly suspected sphenoid si-
inusitis as the cause of the headache and facial pain. The patient un-
derwent emergency endoscopic surgery and was treated with van-
comycin (40 mg/kg/day) and metronidazole (30 mg/kg/day). A
large amount of pus was drained from the right ethmoid and sphen-
oid sinuses; however, no bacteria was cultured from his specimen.
After surgical intervention, all of the symptoms, including the fever,
improved rapidly. He was discharged on the 9th day of admission
without complications. Written informed consent by the patients
was waived due to a retrospective nature of our study.

Our case met the IHS criteria for “headache attributed to acute
rhinosinusitis” in terms of the ipsilateral location of the headache
(right temporal and retro-orbital regions), purulent material in the
right ethmoid and sphenoid sinuses, and the symptoms improved
immediately after surgical drainage of the sinuses. Other several
symptoms and signs also support sinusitis as the cause of his head-
ache: no previous headache history, progressive headache with fe-
ver, worsening pain in lying down position, and the MRI findings
of paranasal sinus pathology. Nevertheless, sinus headache was not
an initial diagnostic impression of this patient.

Sinusitis rarely causes headache when the sinus in question can-
not drain [2]. Purulent nasal discharge is the exception rather than
the rule in sphenoid sinusitis [3] The typical location of headache
associated with sphenoid sinusitis is the vertex, and the pain may
be hemicranial [3]. However, it should be noted that the presence
of nasal discharge and headache location in relation to specific si-

Fig. 1. T2-weighted flair magnetic resonance imaging revealed
opacity in the ethmoid and sphenoid sinuses, with more severe
involvement of the right side.

nus structures as signs of sinus headache were omitted from the re-
vised IHS classification system [4]. Conversely, the presence of su-

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References

Munchausen syndrome is a rare factitious disorder, characterized by either the intentional manifestation of physical symptoms or repeated self-injuries in order to achieve health care attention, complemented by pathological lying and a restless wandering from hospital to hospital for medical and/or surgical interventions [1]. Along with wounds and psychic symptoms, one of the commonest presenting complaint is seizures [2].

Here, we document an interesting case, presenting as factitious psychogenic nonepileptic paroxysmal episodes and limb paralysis.

An 18-year-old male visited the emergency room (ER) with postictal limbs paralysis. Witnesses reported that he suffered a generalized tonic seizure-like event, followed by paraplegia or quadriplegia on resumption of consciousness. Social history revealed that his parents divorced when he was 8 years old and he was subsequently raised by his grandmother. From 9 years of age, he frequently visited ER for varying complaints, including lower extremity arthralgia, chest palpitation, and dyspnea. However, investigations did not show any abnormality. Past surgical history consisted of three episodes of orthopedic surgery and an appendectomy with a grossly normal appendix. He developed his first paroxysmal behavior at the age of 13. While the clinical semiology was bizarre, with brief tremulous movements and the absence of drooling or lip cyanosis, his brain magnetic resonance imaging (MRI) and interictal electroencephalography (EEG) were normal. The caregiver always described it like convulsion and was overly concerned about the child’s strange appearance. So we were forced to start epilepsy treatment. Not surprisingly we unsuccessfully tried several anticonvulsants. Because of repeated episodes and need for active management, he was eventually received the vagus nerve stimulation therapy.

Interestingly, he also experienced several episodes of lower extremity paralysis after seizure-like event, from which he miraculously recovered without any lingering neurologic deficit. A wide array of tests was frequently done, including spinal cord MRI, cerebrospinal fluid analysis, motor and somatosensory evoked potential test, and nerve conduction study. While the patient reported limb paralysis, none of the results were abnormal.

Currently, we performed continuous video EEG monitoring, in anticipation of a seizure. However, he showed non-epileptic behaviors, without suspicious EEG changes (Fig. 1). More importantly, he was discharged 1 hour later, without any neurologic deficit. Eventually, the Anticonvulsants was reduced, and neuropsychiatry clinic was recommended. He never visited our hospital again. His recurrent episodes of simulation of epileptic attacks with limb paralysis and rapid recovery, in the presence of normal investigations, were highly suggestive of Munchausen syndrome.
Patients with Munchausen syndrome have an underlying desire for attention, sympathy, compassion, and in some cases addictive medicine, invasive examinations and operations \([3,4]\). Even in the absence of obvious external rewards from their behavior, they just satisfy with the sick role. While their motivation is frequently unknown, some psychosocial features such as early losses via death, sickness, or abandonment; disrupted attachments to others due to neglect, abuse, or other traumas; are usually common in patients with the disorder \([4,5]\). Therefore, early diagnosis is important and requires the systematic collection of relevant information, including a detailed chronology of the patient’s past medical history and a careful scrutiny of his medical record. Moreover, a supportive relationship has to be established with the patient and his family in order to increase compliance to psychotherapy. It is important that epileptologists keep Munchausen syndrome as part of their differential diagnosis in patients presenting with an unusual seizure semiology or medical history. In such cases, short-term video EEG monitoring with verbal suggestion is a useful and cost-effective diagnostic test.

**Conflicts of interest**

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

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Conceptualization: WSK. Supervision: WSK. Investigation: JSK. Visualization: JSK. Writing: JSK.

**References**

Instructions to authors

Enacted: January 31, 2019

General information

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

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

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

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The title page should contain the following information: (1) title; (2) author list (full names of authors); (3) name of the institutions
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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.
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