Aims and scope

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

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

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# ANNALS OF CHILD NEUROLOGY

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Interleukin-1 in Febrile Infection–Related Epilepsy Syndrome

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Febrile infection–related epilepsy syndrome (FIRES) characteristically affects previously healthy children, who experience a sudden and explosive onset of super-refractory status epilepticus preceded by febrile infection and accompanied by fulminant neurogenic inflammation. FIRES, however, can affect individuals of all ages and is a subcategory of new-onset refractory status epilepticus. This definition of FIRES excludes febrile status epilepticus in infants. FIRES is a rare type of epileptic encephalopathy with rapidly progressive onset of seizures and a devastating prognosis, as drug-resistant epilepsy often follows without a latency period. Although the exact pathogenesis of FIRES has not been elucidated, a functional deficiency in the endogenous interleukin-1 receptor antagonist has been implicated in a genetic predisposition to FIRES. Dysregulation of the interleukin-1β–interleukin-1 receptor 1 (IL-1β–IL-1R1) signaling pathway appears to be involved in the pathogenesis of FIRES. In this review, the authors summarize the definition of FIRES, IL-1β–IL-1R1 signaling, the nucleotide-binding oligomerization domain the NLRP3 inflammasome, and IL-1 targeted therapy for FIRES.

Keywords: Drug resistant epilepsy; Fever; Interleukin-1beta; Interleukin 1 receptor antagonist protein; Inflammasomes

Introduction

Febrile infection-related epilepsy syndrome (FIRES), a subcategory of new-onset refractory status epilepticus (NORSE), is a rare and devastating neurological condition with a high incidence of mortality and poor neurocognitive outcomes [1]. The estimated incidence of FIRES is one in a million, and its prevalence is one in 100,000 [2]. The historical mortality rate for FIRES during the acute phase is 9% to 18%. Additionally, only 18% of children maintain normal cognitive function in the acute phase, while more than 90% develop refractory epilepsy that requires lifelong treatment [1-3].

FIRES tends to affect children and young adults suddenly and explosively following a recent febrile illness. It often begins as new-onset intermittent seizures. The seizures subsequently increase in frequency and duration, and then progress to refractory status epilepticus (RSE) over 2 to 7 days with minimal response to anti-seizure medications (ASMs). Common features reported on electroencephalography in children with FIRES include (1) extreme delta brush; (2) a gradual increase in seizure burden; and (3) focal seizure activity, with an onset low-amplitude fast (>10 Hz) activity that evolves and shifts from one hemisphere of the brain to the other, eventually ending in the contralateral hemisphere [4]. Eventually, seizure activity weakens, and consciousness of varying degrees is gradually restored in surviving patients. Unfortunately, surviving patients often develop severe cognitive decline and
chronic refractory epilepsy [5,6].

A crucial role of interleukin-1β (IL-1β) in FIRES has been demonstrated in case reports describing the effective clinical use of anakinra, a recombinant IL-1 receptor antagonist (IL-1Ra) [1,7]. Moreover, the levels of endogenous IL-1Ra and IL-1β were elevated both in the serum and cerebrospinal fluid (CSF) of patients with FIRES (n=7) relative to healthy controls (n=14, n=7 for CSF) [7]. Specifically, CSF IL-1Ra levels were markedly elevated in patients with FIRES [7]. These results suggest that the IL-1β–IL-1 receptor type 1 (IL-1R1) signaling pathway may play an important role in the pathogenesis of FIRES, and a better understanding of IL-1 in FIRES is needed to improve the treatment of FIRES patients.

**Diagnosis of FIRES**

A consensus-defining group convened and set standard definitions for NORSE and FIRES to unify clinicians and streamline research on NORSE and FIRES in 2018 [8]. NORSE was defined as a clinical presentation, not a specific diagnosis, involving the new-onset of a persistent refractory state of epilepsy without clear acute or active structural, toxic, or metabolic causes in patients without active epilepsy or other pre-existing associated neurological disorders. The International League Against Epilepsy defines FIRES as a subcategory of NORSE that requires a prior febrile infection, with fever starting between 2 weeks and 24 hours prior to the onset of RSE, with or without fever at the onset of status epilepticus [8]. FIRES includes all ages and excludes most cases of febrile status epilepticus in young children (prolonged febrile convulsions). This is because febrile seizures usually occur in children whose fever begins 24 hours before the seizure or is recognized only after the onset of the seizure [9]. Although this definition may include some unusual cases of “febrile status epilepticus” in which a fever persists for more than 24 hours and status epilepticus is refractory, this situation may reflect pathophysiology similar to that of other cases presenting with NORSE, despite being on the mild end of the spectrum. Unlike NORSE, FIRES affects slightly more boys than girls, and the median age of onset is approximately 8 years [8,10].

**Basic Pathogenesis of FIRES: Blood–Brain Barrier Disruption and Neuroinflammation**

The exact pathogenesis of FIRES has yet to be elucidated, although fulminant inflammation in the brain has been implicated [2,11]. Neurogenic inflammation has been proposed to occur as an inflammatory response in cells within the central nervous system (CNS), not only in neurons and glia, but in perivascular cells of the blood-brain barrier (BBB) [12]. A nonspecific, febrile infectious process occurs within 2 weeks before seizure onset. However, no single causative pathogen has been identified [5]. Rather, it is likely that a nonspecific infection, not causal to the syndrome, triggers an inflammatory cascade [5]. The hypothesis, supported by increased CSF levels of inflammatory molecules and the therapeutic response to immunomodulatory therapy, is that progressive febrile infection induces an inflammatory response that reduces the seizure threshold, stimulating the brain of predisposed individuals [1]. Days to weeks after the febrile infection, the reduced threshold favors the precipitation of seizures, triggering a massive neurogenic inflammatory response [1]. These responses contribute to seizure recurrence and status epilepticus [1]. Low rates of multiple autoantibodies, including glutamine decarboxylase, glutamate receptor subtype 2, glutamate receptor subtype 3, anti-voltage-gated potassium channel complex, and neuropil, have been detected in FIRES cases [1,5,13]. However, these rare positive findings appear to reflect nonspecific, secondary epiphenomena associated with BBB breakage [5,13].

**IL-1 and Its Relevance: IL-1, IL-1R1, IL-1Ra, and NLRP3**

IL-1 is the master cytokine of local and systemic inflammation. IL-1Ra is an endogenous competitive antagonist of IL-1R1. This receptor transduces cellular signals upon agonist activation. Over 100-fold molar excess of IL-1Ra is required to inhibit IL-1 activity efficiently [14]. The production of IL-1 is stimulated by exogenous Toll-like receptor (TLR) agonists or endogenous cytokines such as tumor necrosis factor-α [15]. Both IL-1α and IL-1β induce themselves, and this self-sustaining induction of IL-1 leads to auto-inflammation. To prevent unwanted release and inflammatory runaway, IL-1β is synthesized as an inactive precursor that is activated following proteolytic cleavage by the intracellular cysteine protease, caspase-1 [16]. In turn, the activation of caspase-1 requires the oligomerization and assembly of the “inflammasome,” a complex of intracellular proteins [16]. Once activated, caspase-1 cleaves the N-terminal amino acid of the inactive IL-1β precursor, enabling the release of this cytokine’s biologically active form. The assembly and activation of the inflammasome represent an important safety mechanism to prevent the deregulated release of IL-1β. Unlimited activation of caspase-1 and secretion of IL-1β induce systemic and multi-organ sterile inflammation, a hallmark of auto-inflammatory diseases [17].

Inflammasomes are cytoplasmic high-molecular-weight protein platforms of caspase-1 activation in response to microbial invasion.
Inflammasomes consist of the nucleotide-binding oligomerization domain-like receptor (NLR) family, the adapter apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and the effector protease caspase-1. The formation of these protein complexes results in the activation of caspase-1, which is involved in the maturation of the proinflammatory cytokines IL-1β and IL-18 into biologically active forms and the cleavage of gasdermin D (GSDMD) to promote pyroptotic cell death (pyroptosis) [18,19]. Among inflammasomes, the nucleotide-binding oligomerization domain (NOD)-, leucine-rich repeat (LRR)-, and pyrin domain (PY-D)-containing protein 3 (NLRP3) inflammasome has been studied extensively and has been found to be activated by a broad spectrum of stimuli (Fig. 1). In general, NLRP3 inflammasome activation is regulated through a two-step process, with priming at the transcriptional and posttranslational levels (signal 1) and assembly by multiple pathways in response to a variety of exogenous pathogen-derived or endogenous danger molecules (signal 2) [18,19].

**IL-1 and Seizures**

The activation of the IL-1β–IL-1R1 signaling pathway in human
IL-1 Targeted Therapy

1. IL-1Ra blocker: anakinra

IL-1Ra is an endogenous member of the IL-1 family that binds to IL-1R1 and blocks the activity of IL-1α and IL-1β [40]. Anakinra is the recombinant human form of IL-1Ra and was first introduced in 1993. Anakinra currently has an established safety profile and known pharmacokinetics with a short half-life, and it is known to be effective in the CNS [41]. Anakinra is used to treat a variety of diseases, from common conditions such as rheumatoid arthritis, gout, and idiopathic pericarditis, to rare hereditary diseases such as hemophagocytic lymphohistiocytosis [41,42]. Certain mutations in diseases such as familial Mediterranean fever and cryopyrin-associated periodic syndrome result in the uncontrolled release of active IL-1β, which clinically results in periodic fevers with systemic and local inflammation [14]. In phase II clinical studies evaluating the use of anakinra for neurological disorders, including acute stroke and traumatic brain injury, patients demonstrated tolerability of the drug even at exceptionally high doses [43,44].

2. The preclinical outcomes of anakinra, an IL-1R blocker, in seizure models

In a temporal lobe epilepsy model of systemic kainic acid (KA) injection in adult rats, intracerebral injections of IL-1Ra decreased seizure onset, the number of seizures, and the time in seizures by 50%. An altered balance between IL-1β and IL-1Ra appears to determine seizure threshold and contribute to ictogenesis [45]. Another study showed that adult mice overexpressing the IL-1Ra in astrocytes by 15-fold were intrinsically more resistant to seizures [46]. Further studies of anakinra, an IL-1R antagonist, in adult rodent models have demonstrated its effect on the incidence, severity, and duration of seizures [47,48]. Anakinra, which also mediates neuroprotection, inhibited seizures induced by bicuculline in an isolated guinea pig brain [49]. The anticonvulsive effect of anakinra was associated with a reduction in IL-1β expression in astrocytes and rescue of BBB permeability dysfunction [50]. Furthermore, the inhibition of IL-1β biosynthesis with the caspase-1 inhibitor VX-765 effectively reduced drug-resistant recurrent seizures in adult epileptic mice [51].

Since FIRES primarily affects children and young adults, it is relevant to highlight experimental studies involving immature animals. Anakinra reduced kindling epileptogenesis in immature rats promoted by lipopolysaccharide (LPS) [52]. Anakinra combined with a cyclooxygenase-2 antagonist given to young postnatal day (P) P21 rats after status epilepticus reduced the severity of subsequent epilepsy; the rats developed a mild form of epilepsy, with a reduction of spontaneous seizure frequency (up to 70%–90%).
The study also observed reduced cell death and behavioral deficits. Immunomodulation afforded neuroprotection and rescued neurological comorbidities [53]. Activation of the IL-1–IL-1R1 axis has been demonstrated in forebrain astrocytes and neurons in immature P14–15 mice models of hyperthermia-induced status epilepticus [54]. The IL-1–IL-1R1 axis has been shown to contribute to both acute seizures and epilepsy development in these models of prolonged experimental febrile seizures [29,54].

Another model is the inflammatory challenge induced by the bacterial product LPS in immature rats [55]. Seizures were triggered later in life by a subconvulsive dose of chemoconvulsant, suggesting that the induction of seizures and long-term neurological sequelae involved inflammatory processes [55]. In particular, immature rats exposed to KA-induced seizures developed age-dependent neuroinflammation in the forebrain at about 2 weeks of age and approached the adult pattern by P21 [56]. This age-dependent pattern may be attributed to a dissociation between KA-induced seizures and activation of transcriptional factors that promote inflammation, such as activator protein-1 (AP-1) or nuclear factor kappa B (NF-kB). The rodent brain is able to exhibit seizure-induced neuroinflammation at an age comparable to school-aged children who are susceptible to developing FIRES [57].

3. Clinical use of anakinra, an IL-1R blocker

1) Case reports

In 2016, the first case of the use of anakinra to successfully treat a 32-month-old girl with FIRES was reported [58]. Her status epilepticus was previously unresponsive to anesthetic agents, midazolam, and phenobarbital. With prolonged treatment with anakinra (5 mg/kg twice daily, maximum; 200 mg) initiated 6 days after status epilepticus onset and multidisciplinary intervention, the patient showed no developmental or cognitive impairment, except for rare focal seizures. After the first case of anakinra use for FIRES, nine cases, in patients ranging from 32 months to 21 years of age, were presented in case reports [58-65]. Anakinra was mostly administered after various treatments, including anesthetics, ASMs, and anti-immunotherapy. The mean medication count before using anakinra was 8.9 ± 2.6 (median, 10; range, 5 to 12). All patients were treated with a ketogenic diet (KD) and steroid therapy. Eight patients (8/9, 89%) received intravenous immunoglobulin, and five patients (5/9, 56%) underwent plasmapheresis. Anakinra was administered at 5 to 20 mg/kg/day for 6 to 540 days after the onset of FIRES. Excluding a case with anakinra use in a chronic state (at 540 days) of FIRES [61], the mean starting time of anakinra was 26.3 ± 13.2 days (median, 30; range, 6 to 43) after seizure onset [58-60,62-65]. Seven patients (7/9, 78%) reached >50% seizure reduction data [66]. Four patients did not reach a 50% reduction. There was one case of drug rash with eosinophilia and systemic symptoms (DRESS) (case no.1) [58]. Otherwise, there were no specific side effects due to anakinra. Four patients (4/9, 44%) recovered their cognitive function to near baseline before the onset of FIRES [58-65].

2) Cohort study

An international cohort study of 25 patients with FIRES treated with anakinra was published in 2020 [66]. The median age of the patients was 8 years (interquartile range, 5.2 to 11), and all were treated with anesthesia for seizure control prior to the start of anakinra. All children received at least four additional ASMs, with seven or more agents failing in 18 (72%) patients prior to anakinra initiation. Anakinra was started at a median of 20 days (interquartile range, 14 to 25) after seizure onset, with an initial median dose of 3.8 mg/kg/day (interquartile range, 3 to 5) and a final median dose of 5 mg/kg/day (interquartile range, 4 to 9). A seizure reduction of >50% at 1 week of anakinra treatment was observed in 11 of 15 patients (73%) with available seizure frequency data. The neurological outcomes were overall poor, and the differences associated with the degree of seizure control were not statistically significant due to the small sample size. A trend toward a more extended period of mechanical ventilation, intensive care unit (ICU) stay, and hospital length of stay was observed in patients without favorable seizure responses. In the evaluation of the Pediatric Cerebral Performance Category (PCPC), six patients had no or mild impairment (PCPC 1–2), six had moderate impairment (PCPC 3), and five had severe impairment or were in a vegetative state (PCPC 4–5). All surviving children had refractory epilepsy. Twelve children returned to school, and 10 required academic accommodations or special education classes. In that study, early anakinra initiation was associated with a shorter period of mechanical ventilation, shorter ICU and hospital lengths of stay, and possibly, seizure reduction. However, the authors could not ascertain the optimal therapeutic window for anakinra treatment [66].

3) Refractoriness to anakinra in FIRES

In the case reports, two out of nine patients were refractory to anakinra. Case no. 6 responded effectively to tocilizumab, an IL-6 receptor antagonist. The patients had elevated IL-6 levels in the CSF, and anakinra was switched to tocilizumab. The seizures improved, but behavioral dysregulation and inattention persisted [62]. Case no. 4 was resistant to various treatments, including deep brain stimulation of the centro-median thalamic nuclei, and remained in a vegetative state with frequent focal seizures (Table 1). Fifteen patients were available in a cohort study with >50% seizure reduction data [66]. Four patients did not reach a 50% reduc-
tion in seizures after 1 week of anakinra treatment \[66\]. In various autoimmune diseases, the response to anakinra is usually evaluated within 1 to 3 months after initiation of treatment \[67\]. In FIRES, an evaluation at 1 week could be too short to determine the efficacy. The anakinra-refractory patients tended to show a longer duration of mechanical ventilation and ICU length of stay, although this difference was not statistically significant \[66\]. The prognosis at discharge was moderate disability, severe disability, vegetative state, or death \[66\]. It is difficult to determine the risk factors for poor response to anakinra due to small patient numbers. However, from the case series and cohort data, poor anakinra response was correlated with a poor prognosis.

4) Anakinra in the international consensus recommendations
The International NORSE Consensus Group published international consensus recommendations for the management of NORSE, including FIRES, in 2022 \[68\]. The consensus was made by a panel of 48 experts. They recommended treatment similar to the acute treatment of RSE during the initial 48 hours. First-line immunotherapy (corticosteroids, intravenous immunoglobulin G, or therapeutic plasma exchange) should be initiated within the first 72 hours of onset of status epilepticus. In cryptogenic NORSE/FURES without clinical features of a specific autoimmune encephalitis syndrome, IL-1Rαs or IL-6 blockers should be strongly considered as second-line immunological treatment \[68\].

4. Long-term use of anakinra
According to the case series (Table 1), four of nine patients continued anakinra until the time of case report publication \[58,60,61,63\]. Case no. 1 showed DRESS syndrome on day 22. After discontinuation of all drugs, the DRESS was improved. From day 54, anakinra was used again, and DRESS did not recur \[58\]. Two patients used anakinra for 22 and 210 days, respectively, and stopped it because of seizure reduction \[59,65\]. Due to ineffectiveness, the other two patients discontinued anakinra at 14 and 90 days of usage (Table 1) \[60,62\].

In 2022, the Paediatric Rheumatology International Trials Organization reported long-term safety data on anakinra in 306 patients with systemic juvenile idiopathic arthritis \[69\]. Among these 306 patients, 46%, 34%, and 28% had been treated for at least 12, 18, and 24 months, respectively. In total, 201 adverse events (AEs), mostly represented by infections, were reported for 509 patient-years (PY) with an overall incidence rate (IR) of 40 per 100 PY. Among 56 serious AEs (IR=11/100 PY), 23% were infections, and 20% were macrophage activation syndrome episodes. The IR of AEs was higher during the first 6 months of anakinra treatment, followed by decreasing IRs during long-term treatment.

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**Table 1. Summary of FIRES patients with anakinra usage**

FIRES, febrile infection-related epilepsy syndrome; Fv, fever; Sz, seizure; S, steroid; I, intravenous immunoglobulin; ID, intellectual disability; P, plasmapheresis; CMN-DBS, centro-median thalamic nuclei deep brain stimulation; tid, ter in die (three times a day); bid, bis in die (twice a day).

Anakinra was continued until the case report was published.
was discontinued in 76% of patients, most frequently in the first 6 months, because of lack of efficacy (43%), remission (31%), or AEs/intolerance (15%). No deaths or malignancies occurred during anakinra treatment [69]. Although similar safety data are not available for FIRES, anakinra might be considered safe in FIRES patients. Long-term follow-up research on anakinra use in FIRES is needed and may be possible via an international registry.

5. Ketogenic diet
KD is an established treatment for drug-resistant epilepsy and is a preferable option for FIRES over a prolonged drug-induced coma [5,70]. Ketone bodies and reactive oxygen species (ROS) modulation could decrease IL-1β levels by inhibiting NLRP3 expression. Beta-hydroxybutyrate (BHB) is the main ketone body resulting from the oxidation of fatty acids in the liver. Several studies have concurred in favor of a direct anti-inflammatory role for BHB by direct inhibition of NLRP3 inflammasome assembly [71,72]. BHB inhibits the cleavage of caspase-1, which turns IL-1β into its active form in LPS-primed mouse macrophages and human monocytes. This effect is independent of fasting-regulated mechanisms known to act on the NLRP3 inflammasome. Moreover, the effect of BHB on caspase-1 activation and IL-1β secretion has been shown in mouse models of Muckle-Wells syndrome, a disorder associated with a pathogenic variant of the NLRP3 gene. Finally, KD and the associated elevation in BHB levels protected mice bearing the missense NLRP3 mutation that leads to familial cold autoinflammatory syndrome [72]. Furthermore, KD can reduce ROS production by promoting mitochondrial biogenesis [73]. ROS can also activate the NLRP3 inflammasome protein, triggering innate immune defenses through proinflammatory cytokines [74].

6. Other possible candidates
The IL-1–IL-1Ra axis is closely connected to the NLRP3 pathway [18]. Lin and Hsu [19] suggested potential therapeutics other than anakinra that might inhibit this pathway. Drugs targeting NLRP3 inflammasome assembly or activation include interferon-1, MCC950 (a highly specific small-molecule inhibitor for NLRP3), and proton pump inhibitors. A monoclonal anti-IL-1β antibody (canakinumab) and IL-1 blocker (rilonacept) can also be considered to block IL-1β activity [19].

Conclusion
Accumulating data support the proposal that the cytokine pathway mediated through IL-1β is involved in both human and animal models of epilepsy, including FIRES. Dysregulation of the IL-1β–IL-1Ra axis and inhibition affects epilepsy and epileptogenesis. These factors can be modified or targeted by therapeutics, including anakinra, which has evidence of potent anti-seizure effects in various experimental models of seizures, affords neuroprotection, and has potential anti-epileptogenic effects.

Conflicts of interest
Joon Won Kang and Sookyong Koh are the editorial board members of the journal, but They was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Author contribution
Conceptualization: SK. Data curation: JWK. Formal analysis: JWK. Funding acquisition: JWK. Methodology: JWK. Project administration: JWK and SK. Visualization: JWK. Writing-original draft: JWK. Writing-review & editing: SK.

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Clinical Efficacy of Near-Infrared Reflectance Imaging and Optical Coherence Tomography in Identifying Ocular Manifestations of Neurofibromatosis Type 1 in Korean Children

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Introduction

Neurofibromatosis type 1 (NF1) is one of the most common autosomal dominant disorders, with an estimated prevalence of about 1 in 3,000 individuals [1]. It is associated with a mutation in neurofibromin, a tumor suppressor protein located on chromosome 17q11.2.

The diagnostic criteria for NF1 were presented in a National Institutes of Health (NIH) statement in 1987. Two or more Lisch nodules in the iris were required as one of the criteria. Recent imaging technologies, such as near-infrared reflectance (NIR) imaging and optical coherence tomography (OCT), have enabled the visualization of choroidal abnormalities or nodules, which manifest as bright, patchy nodules in most NF1 patients. Therefore, the criteria for NF1 were revised in 2021, adding “two or more choroidal abnormalities” as an ophthalmologic criterion [2]. Our group first reported choroidal nodules in a middle-aged Korean NF1 patient [3], but knowledge of choroidal nodules as an ocular manifes-
tation in Korean NF1 patients has remained limited. Therefore, the present study investigated the clinical efficacy of NIR imaging and OCT to identify choroidal abnormalities in Korean children with NF1. Additionally, the frequency of choroidal abnormalities in Korean children with NF1 was investigated and compared with that of Lisch nodules.

Materials and Methods

This retrospective study was conducted at the Department of Ophthalmology at Inje University Sanggye Paik Hospital. It was approved by the Institutional Review Board of Inje University Sanggye Paik Hospital (approval number: 2022-04-001) and adhered to the Declaration of Helsinki. Written informed consent by the patients was waived due to a retrospective nature of our study.

This study included 10 eyes in five Korean children with NF1 (<18 years old) who had undergone NIR imaging or OCT scans (Heidelberg Engineering, Heidelberg, Germany) at the Department of Ophthalmology, Inje University Sanggye Paik Hospital, from January 2014 to April 2022. The diagnosis of NF1 was based on the stringent NIH criteria. All patients also underwent ophthalmic procedures, including slit-lamp examinations, NIR imaging, OCT scanning, and fundus examinations other than by NIR imaging or OCT.

Results

The data on the patients and their eyes are shown in Table 1. At the first visit, Lisch nodules were found in only two eyes. After our initial report on choroidal nodules found in a middle-aged Korean NF1 patient, NIR imaging and OCT scans were taken for pediatric NF1 patients in the course of their follow-up. Choroidal nodules were found in all eyes of all patients. Slit-lamp examinations performed on the same day as NIR imaging and OCT scans revealed two, one, two, and three Lisch nodules unilaterally in cases 1, 2, 3, and 5, respectively. To fulfill the criteria for NF1, two or more Lisch nodules are needed; however, in case 2, only one Lisch nodule was found, and in case 4, there was no Lisch nodule.

1. Case 1

A 4-month-old girl visited our clinic for congenital nasolacrimal duct obstruction. More than 15 café-au-lait spots larger than 5 mm in the greatest dimension and freckling on the right axilla were discovered, though no slit-lamp examination could be performed due to poor cooperation. She visited our clinic regularly thereafter. When she was 2 years old, no Lisch nodule was found on her first slit-lamp examination, but one neurofibroma had newly appeared in the left hand.
on her left hand. When she was 4 years old, her best-corrected visual acuity (BCVA) was 20/25 in the right eye and 20/50 in the left eye. One Lisch nodule was initially found in her right eye. Color fundus photography appeared normal in both eyes (Fig. 1A). One year later, two Lisch nodules were discovered in her right eye, whereas her left eye still showed no Lisch nodules. NIR imaging and OCT scanning were performed, revealing two choroidal nodules in the right eye, and three choroidal nodules, one of which was located within the macular area, in the left eye (Fig. 1A). OCT scans of the area of high reflectance in NIR imaging clearly showed the presence of a choroidal nodule with an irregular hyper-reflectance focus confined to the choroid (Fig. 1A). After another year, her BCVA was 20/25 in both eyes.

2. Case 2
A 5-month-old boy with more than 10 café-au-lait spots larger than 5 mm was referred to our clinic for NF1 evaluation. There were no Lisch nodules on the initial visit. After that, he had regular check-ups every 6 months. When he was 1 year old, one neurofibroma was newly found at the nape of his neck. The BCVA, which was measured at 3 years old when he was able to cooperate, was 20/20 in both eyes. When he was 5 years old, one small hypo-pigmented nodule was found in the iris of his right eye. No Lisch nodules were found in the left eye. Color fundus photography showed no abnormalities (Fig. 1B). When the first NIR imaging and OCT were performed at the age of 8, four small choroidal nodules in the right eye and two choroidal nodules in the left eye were found (Fig. 1B). No additional Lisch nodules appeared in the course of his follow-up.

3. Case 3
A 4-year-old boy visited our clinic for esotropia. He had more than...
10 café-au-lait spots larger than 5 mm, freckles in the axilla, and had already been diagnosed with NF1 at another hospital. The BCVA was 20/25 in both eyes, and the alternative prism cover test showed 15-prism diopter left esotropia at distance and near. A slit-lamp examination revealed two Lisch nodules in the right eye, whereas no Lisch nodules were apparent in the left eye. No abnormalities were found on color fundus photography (Fig. 1C). NIR imaging and OCT after a month showed three choroidal nodules in the right eye and one small choroidal nodule in the left eye (Fig. 1C). After another 3 months, a Lisch nodule was newly found in the left eye.

4. Case 4
A 5-year-old boy was referred to our clinic for NF1 evaluation. He had 14 café-au-lait spots larger than 5 mm, freckles in the axilla, and two neurofibromas in the anterior abdominal wall, and his mother had already been diagnosed with NF1. On the first visit, the BCVA in both eyes was 20/20. There were no visible Lisch nodules. He underwent the first NIR imaging and OCT scans 3 years after the first visit, which showed one choroidal nodule in the right eye and two choroidal nodules in the left eye. One of the choroidal nodules in the left eye was located within the macular region (Fig. 2A). Color fundus photography, taken on the same day, was normal (Fig. 1D). In the course of follow-up every 6 months, Lisch nodules still were unobserved. However, the choroidal nodules became more apparent. When he was 12 years old, the number of choroidal nodules had increased to 2 in the right eye and 3 in the left eye on NIR imaging (Fig. 2B).

5. Case 5
A 9-year-old boy, the sibling of case 4, was referred to our clinic for NF1 evaluation. He had 21 café-au-lait macules larger than 5 mm, freckles in the axilla and groin, and one neurofibroma on the ankle. The BCVA of both eyes was 20/20. There were no Lisch nodules

Fig. 2. In case 4, the number of choroid nodules increased over time. (A) The first near-infrared reflectance images were taken when the patient was 8 years old, showing one choroidal nodule in the right eye and two choroidal nodules in the left eye. (B) After 4 years, two choroidal nodules in the right eye and one choroidal nodule in the left eye newly appeared (arrows).
in the right eye, and two Lisch nodules were observed in the left eye. He revisited our clinic after 5 years. Lisch nodules remained absent from the right eye, while one additional Lisch nodule had appeared in the left eye, for a total of three. Color fundus photography was normal in both eyes (Fig. 1E). He underwent NIR imaging and OCT scanning on the same day, whereupon two choroidal nodules in the right eye and seven choroidal nodules in the left eye were found (Fig. 1E). Regular follow-up was done every 6 months, and by the time the patient was 15 years old, one Lisch nodule had appeared in the right eye.

**Discussion**

Our study, which is the first report on choroidal nodules in a case series involving Korean NF1 patients, showed that choroidal nodules outnumbered and developed earlier than Lisch nodules in Korean children with NF1. According to the previous diagnostic criteria developed at NIH in 1987, Lisch nodules, optic pathway glioma, and osseous lesions are the only extracutaneous signs of NF1. However, it is important to consider that Lisch nodules are often undetectable in early childhood [4]. Lisch nodules are uncommon before 2 years of age and are only occasionally observed before 6 years of age. The prevalence, number, and dimensions of Lisch nodules are known to increase significantly with age [5]. In our study, Lisch nodules were found only in two eyes, in cases 3 and 5, at the initial visit. Lisch nodules newly appeared in two eyes in both cases 1 and 2 during the follow-up period. In case 5, the number of Lisch nodules increased from 2 to 3 after 5 years. These Lisch nodules were found only unilaterally in four of the five children with NF1, and in one child (case 4), no Lisch nodules had appeared by the final follow-up. These results are entirely consistent with the established facts that Lisch nodules are rarely detected at a young age and that their prevalence and number increase with age. The incidence of optic pathway gliomas ranges from 15% to 20% in NF1 patients [6], and in our case series, none of the patients were diagnosed with optic pathway glioma.

After the introduction of new ophthalmic imaging modalities, it became known that choroidal abnormalities are found in most NF1 patients. Yasunari et al. [7] reported a 100% prevalence of choroidal abnormalities in 17 NF1 patients. Viola et al. [8] published the largest cross-sectional study on this topic, which included 95 NF1 patients and 100 healthy control subjects; choroidal nodules were detected by NIR in 82% of the NF1 population, including 71% of a pediatric NF1 population aged 12 years or younger. The diagnostic accuracy was 90% in the overall population and 83% in the pediatric population [8]. Goktas et al. [9] reported a prevalence of 78.9% in a pediatric population of 19 patients aged 4 to 16 years. Parrozzani et al. [10] published the largest pediatric cohort study, which included 140 pediatric NF1 patients, 59 NF1-suspected patients and 42 healthy subjects; choroidal abnormalities were found in 60.5% of the affected and 2.4% of the suspected patients. Vagge et al. [11] reported nodules in 69.2% of 78 patients with a mean age of 8.1 ± 3.5 years. Cassiman et al. [12] reported nodules in 65% of 34 patients.

When NIR imaging and OCT scans were performed for our cohort, which included five Korean patients with NF1, choroidal nodules were found in all eyes. Among the studies published so far, a 100% prevalence of choroidal abnormalities in NF1 patients was reported only by Yasunari et al. [7], who evaluated 17 Japanese patients. These results show that the prevalence of choroidal abnormalities is significantly higher in Asian patients. Race might be one of the factors affecting the detection of choroid nodules using NIR imaging. This might be due to racial differences in choroidal melanin content [13]. In some cases reported in European countries, such as the one reported by Cassiman et al. [12], choroid nodules were visible in color fundus photography. However, no abnormalities were noted in color fundus photography in our cases or in the cases of Yasunari et al. [7]. These findings imply that NIR imaging and OCT scans are critical diagnostic tools for NF1 in Asian patients.

Slit-lamp examinations performed on the same day as that of the NIR imaging revealed that only four of the 10 eyes had Lisch nodules. This finding coincides with the previous report that the prevalence of choroidal nodules detected by NIR (71%) was much higher than that of Lisch nodules (43%) in pediatric NF1 patients [8], and implies that the choroid seems to be one of the most commonly affected tissues by NF1. A previous histologic study showed thickening of the posterior retina in NF1 patients, which was caused by a proliferation of neural-crest-derived melanocytes and neural cells in the choroid [14]. A high melanin concentration due to an increased number of neural-crest-derived melanocytes might induce strong backscattering to NIR lights, which in turn might enable choroidal nodules to be more visible in NIR imaging than in color fundus photography [15]. Spectral-domain OCT scans taken simultaneously with NIR imaging in an earlier study showed that choroidal abnormalities in NIR images were confined to the choroid [8].

NIR imaging is a valuable diagnostic method for pediatric NF1 patients because it is sufficiently sensitive to detect early-developed ocular signs and can be obtained in a short time without glare.

In cases 1 and 4, one of the choroidal nodules was located within the macular region. The BCVA of the affected eye was 20/25 in case 1 and 20/20 in case 5, which was the same as the opposite eye. This shows that the choroidal nodules did not affect vision. Fur-
ther evaluation, such as a visual field test, might be helpful to support this conclusion.

Our study is limited by its small sample size, since only five patients were included. Furthermore, some of the examinations related to NF1, such as genetic tests, were not fully done in our clinic. However, these five patients fulfilled at least two of the clinical manifestations to be diagnosed as NF1.

In conclusion, choroidal nodules are a more common and earlier-detected ocular manifestation than Lisch nodules in Korean children with NF1. NIR imaging enables quick, reliable, non-invasive examinations of the choroid to detect choroidal abnormalities; as such, it may be useful for diagnosing NF1 in patients who are young and/or lack cooperation. Further, NIR imaging along with OCT can help to localize choroidal nodules in NF1 patients.

Conflicts of interest

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

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Author contribution

Conceptualization: WHO and JC. Data curation: JMP and JC. Formal analysis: JMP, WHO, and JC. Visualization: JMP. Writing-original draft: JMP. Writing-review & editing: WHO and JC.

References

Clinical Profile of Children with Primary Headache at a Tertiary Care Center in North India: A Retrospective Study

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Purpose: The present study investigated the clinical profile of children with primary headache at a tertiary care center in North India.

Methods: A retrospective observational study was conducted between January 2021 and October 2022. In total, 100 children 5 to 18 years of age who attended the pediatric outpatient department or the emergency department with primary headache were included. Children with secondary causes of headache were excluded.

Results: This study included 100 children (40 boys, 60 girls), and the female-to-male ratio was 1.5:1. The patients ranged in age from 5 to 18 years (mean ± standard deviation, 10.1 ± 2.8). Migraine headaches were most commonly reported (60%) followed by tension-type headache (28%) and others (12%). The throbbing type of pain was most common (43%), followed by the tightening type in 32%. The pain location was bilateral frontal in 47% of patients, followed by bitemporal in 20% and occipital in 17%. Most of the children (87%) had a headache duration of 2 to 4 hours. The common precipitating factors were skipped meals (25%), bright light (18%), lack of sleep (16%), and schoolwork (15%). A family history was present in around 62%. Around 70% of children required prophylactic medications (flunarizine and propranolol). Long screen time (2 to 4 hours/day) and a family history of headache were significantly associated with primary headache (P<0.05).

Conclusion: The present study highlights that migraine is the most common cause of primary headache in children, and every effort should be made for the early detection and management of headaches among children.

Keywords: Headache; Migraine disorders; Tension-type headache; Screen time

Introduction

Headache is the most common neurological symptom manifesting as pain in childhood [1,2]. The diverse causes, frequency, and intensity of headache have a major impact on children's intellectual performance, memory, personality, and school attendance [3-5].
Healthcare providers should be able to differentiate between primary and secondary headaches so that more sinister causes can be treated as early as possible, thus improving quality of life and minimizing disability [6]. The frequency of headache increases with age, and the underlying causes range from migraine and tension-type headaches (TTH) to life-threatening infections and brain tumors [7]. The reported prevalence of primary headache is 10% to 20% in school-aged children [8,9] and > 50% in those under 20 years of age [10]. Data on pediatric headache in India are limited to a few school-based questionnaire surveys [11,12], case series of specific primary headaches, or isolated case reports of rare headache types [11]. Most childhood headaches are due to a primary headache disorder, such as migraine, or an acute benign process, such as viral infection. However, more serious causes of headache should always be ruled out [13]. Migraine remains the most common type of pediatric headache disorder, for which caregivers seek doctors’ opinions. A detailed evaluation of headache in the pediatric population is necessary for proper diagnosis and management.

The present study aimed to investigate the clinical profile and factors associated with primary headache in children at a tertiary care center in North India.

Materials and Methods

1. Study design
A retrospective, observational study was conducted at a tertiary care center in North India from January 2021 to October 2022. Children between 5 and 18 years of age who attended the pediatric outpatient department or the emergency department with primary headache were included in the study. Children presenting with headache due to fever, trauma, and/or other obvious causes, such as meningitis, dental conditions, and sinusitis, were excluded. This study was approved by the Institutional Review board of Command Hospital, Chandimandir (letter no. 14/03/CHWC/2022). The written informed consent by the patients was waived due to a retrospective nature of our study.

2. Case selection
Children between the ages of 5 and 18 years with headache who visited the pediatric outpatient department or the emergency department of the hospital from January 2021 to October 2022 were identified using the hospital case sheets. The medical records of all these children were reviewed, and patients with primary headache whose records were complete were included in the current study. Children with diseases that could potentially be associated with secondary headache, such as brain tumors, sinus infections, dental related disease, febrile illness, other systemic diseases, and eye problems were excluded. Patients’ data were evaluated based on the medical records from the first visit. The diagnosis and classification of headache followed the International Classification of Headache Disorders (ICHD-3) beta version criteria applied to children and adolescents. We divided headaches into three groups: migraine, TTH, and other causes of headache. The documented patients’ data included demographic profile (such as age and sex) and clinical information (such as the location of the headache, character, duration, frequency, precipitating factors, family history, prophylactic medications, screen time), and headache severity (using a visual analogue scale in patients over 6 years of age and a face pain scale for children less than 6 years of age). The investigations included detailed eye evaluation, neuroimaging, electroencephalogram (EEG), and the house-tree-person (HTP) psychological test for any stressors. Data from all 100 children were noted in a Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA, USA) and analyzed for predefined variables.

3. Statistical analysis
The collected data were recorded in a Microsoft Excel spreadsheet. The statistical analysis was performed using SPSS version 20 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as number and percentage, while continuous variables were presented as mean and standard deviation. The chi-square test was used to assess the associations of categorical variables with recurrent headache. A P value < 0.05 was considered statistically significant.

Results

During the study period, 118 children presented with headache, of whom 18 were excluded from the study. Ten of them did not have appropriate medical records, while eight of them had secondary headache. The study flow is depicted in Fig. 1. The demographic data and clinical data are depicted in Tables 1 and 2, respectively. They ranged in age from 5 to 18 years (mean ± standard deviation, 10.1 ± 2.8). Boys (40/100) and girls (60/100) were distributed at a ratio of 1:1.5. Sixty percent of the patients had migraine (60/100), while 28% of the patients had TTH. The frontal location predominated in both groups, with a higher proportion in the migraine group (55%, 33/60) than in the TTH group (35.7%, 10/28). The most common character of the headache was throbbing in all three groups (P < 0.05). The proportion ranged from 32.1% (9/28) in the TTH group to 66.7% (8/12) in the “others” group. The duration of headache in most patients was between 2 and 4 hours. The proportion of patients with headache lasting more than 4 hours was only 18.3% (11/60) in the migraine group and 7.2% (2/28) in
Children between 5 to 18 years of age who attended the Pediatric and Emergency Department with recurrent headache (n=118)

Application of inclusion & Exclusion criteria

Study population (n=100)

The documented patient’s data included demographic profile, clinical and investigations details. Data of all 100 children were noted in excel sheet and analysed on predefined variables.

Excluded (n=18)
Children with secondary headache (n=8)
Inadequate medical record (n=10)

Fig. 1. Flow of study.

the TTH group. The frequency of headache was either weekly or monthly in the majority of the patients. Various precipitating factors were found. Missing meals was the most common precipitating factor for headache in all three groups. Other common precipitating factors were family issues related to stressors in studies, academic difficulties, bright light, specific food items, sleep deprivation, and others. Almost half of the patients with migraine (25/60) scored the severity of their headache in the range of 3 to 5, while most patients with TTH scored their headache in the range of 6 to 8 (18/28). As far as the screen time was concerned, 58.3% of the children with migraine reported screen time of 2 to 4 hours. Most of the children with TTH reported screen time of either less than 2 hours (10/28) or more than 4 hours (10/28).

Neuroimaging was not done in nearly half the patients in the migraine and TTH groups. However, 66% of the children who were categorized under “others” were advised to undergo brain magnetic resonance imaging and all the patients had normal neuroimaging. Among the patients who underwent neuroimaging, the proportion of children with non-specific white matter signal changes was 26.7% and 14.3% in the migraine and TTH groups, respectively. The eye evaluation and EEG study were normal in the majority of patients in all three groups. The children with abnormal EEG findings never had seizure episodes. The HTP test revealed stressors in 41.7%, 35.8%, and 16.7% of patients in the migraine, TTH, and others groups, respectively. A positive family history of primary headache was found in 75% of the patients in the migraine group, while the proportion was 53.6% in the TTH group (Table 3).

Discussion

Headache has a major impact on children’s intellectual performance, memory, personality, and activities of daily living. Very scant literature is available on the prevalence of pediatric headache in India and the factors responsible for recurrence of primary headache. Questionnaire-based studies provide more reliable information and are feasible, yet clinical interviews are the gold standard for such studies [8]. In our study, we retrospectively analyzed the clinical data of children with recurrent headache. Similar to the existing literature [8,10,11], we observed that the prevalence of headache was higher in girls than in boys. Both migraine and TTH were found to be more common in girls.

In our study, the prevalence of migraine was 60% and TTH was 28% among children presenting with complaints of recurrent headache. These prevalence rates were much higher than those of 6% to 10% for migraine and 15% to 18% for TTH reported in previous studies, with migraine being the common sub-type of headache in children, followed by TTH [13-15]. The wide variation in the prevalence rates could be because those studies involved questionnaires administered to all school-going children, while ours is based on the retrospective analysis of clinical data of children presenting with headache in our clinical setting. The variation also could be because our study was conducted in different geographical region from the previous studies. The disparity in the prevalence rates could be due to ICHD-3 definitions used in our study, which were not used in the previous studies, which were conducted prior to the implementation of the ICHD-3 criteria. However, a questionnaire-based Indian study by Gupta et al. [8] conducted among school-going children showed a high prevalence of both migraine and TTH, with migraine being more common than...
Table 1. Patients’ demographic and clinical characteristics

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<th>Characteristic</th>
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<th>Tension-type headache (n=28)</th>
<th>Others (n=12)</th>
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<td>6.9±1.3</td>
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<tr>
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<td>27 (45)</td>
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<td>3 (25)</td>
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<tr>
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<td>33 (55)</td>
<td>18 (64.3)</td>
<td>9 (75)</td>
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<tr>
<td>Duration of pain (hr)</td>
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<tr>
<td>1–2</td>
<td>24 (40)</td>
<td>12 (42.8)</td>
<td>8 (66.7)</td>
<td></td>
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<tr>
<td>2–4</td>
<td>25 (41.7)</td>
<td>14 (50)</td>
<td>4 (33.3)</td>
<td></td>
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<tr>
<td>&gt;4</td>
<td>11 (18.3)</td>
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<tr>
<td>Frequency</td>
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<tr>
<td>Daily</td>
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<tr>
<td>Weekly</td>
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<td>13 (46.4)</td>
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<tr>
<td>Monthly</td>
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<tr>
<td>3-monthly</td>
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<td>2 (7.2)</td>
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<td>Precipitating factors</td>
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<td>Lack of sleep</td>
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<td>Academic issues</td>
<td>9 (15)</td>
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<tr>
<td>Missing meals</td>
<td>16 (26.7)</td>
<td>6 (21.4)</td>
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<tr>
<td>Bright light</td>
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<td>7 (25)</td>
<td>2 (16.7)</td>
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<tr>
<td>Food-related</td>
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<td>Headache severity score</td>
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<tr>
<td>3–5</td>
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<td>6 (50)</td>
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<tr>
<td>6–8</td>
<td>19 (31.7)</td>
<td>18 (64.3)</td>
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<td>0</td>
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<tr>
<td>Screen time (hr)</td>
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<tr>
<td>&lt;2</td>
<td>10 (16.7)</td>
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<td>5 (41.7)</td>
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<tr>
<td>2–4</td>
<td>35 (58.3)</td>
<td>8 (28.6)</td>
<td>2 (16.6)</td>
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<tr>
<td>&gt;4</td>
<td>15 (25)</td>
<td>10 (35.7)</td>
<td>5 (41.7)</td>
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<tr>
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<td>2 (16.7)</td>
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<tr>
<td>No</td>
<td>15 (25)</td>
<td>13 (46.4)</td>
<td>10 (83.3)</td>
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</tr>
</tbody>
</table>

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

*a Chi-square test (P<0.05 significant); b Face pain scale (<6 years of age) and visual analogue scale (>6 years).

TTH, similar to our findings. In most of the children, the headache was localized to the frontal region in both migraine and TTH, contrary to the general view of a “constricting band”-like diffuse headache in TTH.

1. Precipitating factors of headache in children and adolescents

Not many studies have compared the precipitating factors of migraine and TTH in children [16]. In our study, we found that hunger (“skipping meals”) was a common precipitating factor for both
the types of headaches. This underlines the need to focus on educating children and parents about maintaining a healthy lifestyle with timely meals. Although in the current study, we did not focus on studying the effect of education of parents on the recurrence of headache episodes, the current findings suggest that further studies are required on this topic. In our study, we also observed that presence of a positive family history predisposed children to recurrent episodes of headache, especially in cases of migraine rather than TTH, similar to previous studies, indicating the presence of an underlying genetic predisposition in the pathophysiology of headaches.

2. Screen time and its effects on headache
Our findings in this study are in agreement with previous research.
in children and adolescents, which observed a relationship between screen time exposure and migraine in those using digital/electronic gadgets routinely [17]. We observed that more than half of the children with migraine had a large amount of screen time (2 to 4 hours). Although we do not have direct insights into the biological basis, it has been hypothesized that the luminosity or frequency of the screen’s light might directly trigger an acute attack of migraine [18]. According to previous studies, no markers have yet been identified that can predict the recurrence of headache in children. A recent study by Lund et al. [19] showed that more screen time was associated with more frequent headaches in children, but the causality of this association was not established. However, in this study, we observed that screen time could be used as a surrogate marker for predicting the recurrence of headache, more so in children with migraine than in those with TTH and other types of headaches. However, larger studies are warranted to substantiate these findings. Nevertheless, focus should be given to highlighting the importance of optimizing the screen time and establishing appropriate etiquette for using screen-based gadgets.

3. The HTP test for stressor identification in patients with headache

The HTP projective drawing test provides clinically meaningful information regarding an individual’s psychological, emotional, and mental health condition. Although a recent study by Lin et al. [20] cast doubt on the validity of the HTP test in predicting mental health, this test has long been used for identifying stressors with good reliability. In our study, the HTP test identified the presence of stressors not only in those with migraine, but also in those with TTH and other forms of headaches.

In conclusion, primary headache disorders were more common than secondary headache, with migraine being the commonest type observed. Headache prevalence increased with increasing age, and girls were more often affected than boys. Prospective studies involving a larger number of children are further warranted. In addition, reducing screen time and not skipping meals should be encouraged for all children with primary headaches.

Conflicts of interest

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

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Author contribution

Conceptualization: RS and DS. Data curation: RS and AU. Formal analysis: GK and SS. Methodology: RS and AU. Visualization: SS. Writing-original draft: RS. Writing-review & editing: GK and SS.

Acknowledgements

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Status Epilepticus in Children: Experience in a Portuguese Tertiary Hospital

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Original article

Purpose: Status epilepticus (SE) is a life-threatening neurological emergency, frequently diagnosed in pediatric patients. We aimed to characterize our pediatric cases of SE in an 11-year period according to the 2015 International League Against Epilepsy report.

Methods: Clinical electronic records were retrospectively reviewed. All pediatric SE cases admitted from January 2010 to December 2020 were included, excluding neonates. SE was considered refractory if it persisted despite the administration of two appropriate antiseizure medications at acceptable doses.

Results: We included 102 episodes, 55 (53.9%) in boys. The median age was 2.5 years (interquartile range, 1.3 to 5.0). Most episodes were classified as SE with prominent motor features (92.2%), and the most frequent etiological classification was acute symptomatic cause (84.3%). A benzodiazepine was used as the first-line antiseizure medication in 99 (97%) cases, of which diazepam was preferred (93%). The preferred second-line medication was phenytoin (65.7%). Midazolam was the most frequently responsible for termination of SE when given in a continuous infusion (47%). Episodes of SE were classified as refractory in 81 (79.4%) cases. Episodes of >60 minutes were more frequent in patients diagnosed with epilepsy (P=0.036), focal motor SE (P<0.001), and non-convulsive SE (P=0.037). The in-hospital mortality rate was 2.9%.

Conclusion: Most of our findings are in accord with the current literature. Epilepsy, non-convulsive SE, and focal motor SE were associated with prolonged duration (>60 minutes), which reinforces the significance of the underlying neurological disease and semiological standardization in pediatric SE.

Keywords: Status epilepticus; Epilepsy; Seizures; Pediatrics

Introduction

Status epilepticus (SE) is a life-threatening neurological emergency, one of the most frequently found in pediatric settings, with an annual incidence of 10 to 73 per 100,000 children [1]. It is a major cause of admission to pediatric intensive care units (PICUs) globally [1].

Our understanding of the pathophysiology of SE has advanced...
significantly in recent years. However, this has not straightforwardly translated to clinical practice and guidelines [2]. In 2015, the International League Against Epilepsy (ILAE) reviewed some clinical aspects and proposed a new definition and classification for SE [3]. The definition states that SE is a condition “resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point 1)... that can have long term consequences (after time point 2)” [3]. For convulsive status epilepticus (CSE), it was suggested that time point 1 is 5 minutes, while time point 2 is 30 minutes [3]. This is extremely important because the timing of antiseizure medication (ASM) is a major determinant for preventing brain injury from excitotoxicity and cell death [4]. The new classification of SE has clinical and epidemiological meaning, and it involves four axes: semiology, etiology, correlates in electroencephalography (EEG), and age [3]. Globally, several research groups have applied these updates by ILAE in their observational studies of SE in children [5-7].

There is not a complete consensus regarding the treatment of SE, and it may vary according to local guidelines [8]. In our country, Portugal, a review of the approach to CSE in children and adolescents was published in 2020 by the Portuguese Society of Neurology [9]. To our knowledge, no observational studies from Portugal have previously applied the latest definition and classification by ILAE.

Therefore, the aim of our study was to characterize clinically and demographically all pediatric cases of SE admitted to our tertiary hospital in an 11-year period. We also aimed to describe the classification of all cases according to the 2015 ILAE report.

Materials and Methods

1. Subjects
The study included all cases of pediatric SE admitted to the urgent care clinic, emergency room, or PICU of our tertiary institution from January 2010 to December 2020. We searched for cases with a discharge code of SE according to the International Classification of Diseases, 10th Revision (ICD-10) and included cases of SE with prominent motor features and non-convulsive status epilepticus (NCSE) with clinical descriptions in accordance with the new definition in the 2015 ILAE report [3]. The diagnosis of NCSE was confirmed by EEG, applying the modified Salzburg criteria [10].

Cases with an initial ICD-10 code of SE were excluded when they could not be diagnosed with SE from a review of the clinical record. Neonates were also excluded from this study, due to their specific characteristics.

2. Research design
We conducted a single-center retrospective study of accessible electronic medical records to describe demographic features and clinical characteristics, as well as management, responsiveness to treatment, and in-hospital outcomes.

3. Variables
The following data were collected for each patient: age and sex; year of admission; previous seizures or SE episodes, epilepsy, and other underlying neurological diseases; circumstances of the event, including place of occurrence and inter-hospital or intra-hospital transfer; clinical features, including duration, semiology, and etiology according to the 2015 ILAE report; antiseizure management including selected ASM (before and after admission) and administration routes; and responsiveness to treatment; and in-hospital outcome (survival).

Semiology was described according to the presence or absence of prominent motor symptoms, and the degree of impaired consciousness [3]. Etiology was determined based on medical history, symptoms, physical examination, and laboratory tests. Etiologies were divided into known (symptomatic) and unknown (cryptogenic). Symptomatic etiologies included acute, remote, and progressive disorders, as well as SE in defined electroclinical syndromes [3]. The duration of SE was clinically assessed and included information from observers about seizure duration before admission. The total duration of SE was categorized as 5–30, 30–60, and >60 minutes. Regarding responsiveness to treatment, SE was classified as refractory if it persisted despite the administration of two appropriate ASMs at acceptable doses [5].

4. Ethics
This study was approved by the Ethics Committee of São João University Hospital Center, Porto, Portugal (No. CE-28-2023). Written informed consent by the patients was waived due to a retrospective nature of our study.

5. Statistical analysis
Data collection and statistical analysis were performed using SPSS version 27 (IBM Corp., Armonk, NY, USA). Categorical variables were described as absolute and relative frequencies, continuous variables with a symmetric distribution by mean ± standard deviation, and continuous variables with an asymmetric distribution by median with interquartile range (IQR). The chi-square test and Fisher exact test were applied to compare categorical variables, and the independent t-test and Mann-Whitney U test were used for symmetric and asymmetric continuous variables, respectively. A P < 0.05 was considered statistically significant.
Results

1. Demographics and clinical characteristics of the cohort
The study cohort included 102 episodes of SE in 99 patients (one patient had two episodes; another patient had three episodes). Fifty-five (53.9%) episodes occurred in boys. Patients’ age ranged from 36 days to 16 years, with a median age of 2.5 years (IQR, 1.3 to 5.0). Episodes of SE occurred at home in 66 cases (64.7%), at the hospital in 22 cases (21.6%), and at unspecified locations in 14 cases (13.7%). Patients were transferred from other hospitals in 64 cases (62.7%) and from other departments of our hospital in 10 cases (9.8%); they came directly from home in 28 cases (27.5%).

The clinical description is summarized in Table 1. Fifty-two patients (52/99; 52.5%) were diagnosed with epilepsy, and six of them (11.5%) had a history of previous SE episodes. In the group of patients with epilepsy, a diagnosis of epilepsy was established prior to admission in 26 patients (50%), during the hospital stay in eight patients (15.4%), and after discharge in 18 patients (34.6%). In 19 episodes (18.6%), patients had additional neurological disorders, such as chromosomal aberrations and intracranial tumors, which condition the presence of epilepsy. Regarding semiology, most episodes were classified as SE with prominent motor features (94/102; 92.2%). The most frequent etiological classification was an acute symptomatic cause (86/102; 84.3%), and an infectious etiology was the most common cause of SE (79/102; 77.5%). All patients with an unknown cause of SE were older than 2 years, and this association was statistically significant (P=0.045).

2. Management and outcome
Sixty-eight (66.7%) episodes occurred in patients admitted to the PICU, while the remaining 34 (33.3%) were admitted to the emergency room or ED. Before admission to our hospital, SE treatment was started in 40 cases (39.2%). In 14 cases (13.7%), the ASM start time was recorded, with a median interval of 17.5 minutes (IQR, 13.8 to 30) after the beginning of SE; all 14 of these cases were CSE. The first ASM used was a benzodiazepine (BZD) in 99 (97%) cases, of which diazepam was the preferred BZD (93%) versus midazolam (7%). All cases in which a non-BZD was the first-line ASM were patients with known epilepsy. Overall, rectal route was preferred for the administration of the first BZD in 65 (65.7%) cases, followed by the intravenous route in 33 (33.3%) cases; intramuscular midazolam was administered in one patient. Before reaching the hospital, the first BZD route was rectal in 67.5% of patients, intravenous in 30% and intramuscular in 2.5%. In the hospital, the first BZD route was rectal in 69.5% of patients and intravenous in 30.5%. There were no statistically significant differences between the administration routes (with vs. without peripheral venous access) and the start of treatment prior to or after admission (P=0.957). A second bolus of BZD was administered in 76 of 99 cases (76.8%), with the same BZD in 68 cases (89.5%). A second bolus of BZD was more frequently administered in patients with episodes of SE occurring at home or other locations outside a hospital (83.6%), but this difference was not.

Table 1. Clinical description of the study cohort (n=102)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
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<td>Additional neurological disorders</td>
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<tr>
<td>Chromosomal aberration/congenital malformation</td>
<td>5 (26.3)</td>
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<tr>
<td>Intracranial tumor</td>
<td>3 (15.8)</td>
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<tr>
<td>Neurodegenerative disease</td>
<td>2 (10.5)</td>
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<tr>
<td>Metabolic disorder</td>
<td>2 (10.5)</td>
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<td>Head trauma</td>
<td>2 (10.5)</td>
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<tr>
<td>Autoimmune disorder</td>
<td>2 (10.5)</td>
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<tr>
<td>Mitochondrial disease</td>
<td>1 (5.3)</td>
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<tr>
<td>Cerebrovascular disease</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Cortical dysplasia</td>
<td>1 (5.3)</td>
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<td><strong>Semiology according to the 2015 ILAE classification</strong></td>
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</tr>
<tr>
<td>With prominent motor features</td>
<td>94 (92.2)</td>
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<tr>
<td>Convulsive SE</td>
<td>75 (79.8)</td>
</tr>
<tr>
<td>Generalized</td>
<td>70 (93.3)</td>
</tr>
<tr>
<td>Focal onset evolving into bilateral</td>
<td>5 (6.7)</td>
</tr>
<tr>
<td>Focal motor</td>
<td>17 (18.1)</td>
</tr>
<tr>
<td>Tonic status</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Without prominent motor features</td>
<td>8 (7.8)</td>
</tr>
<tr>
<td>Non-convulsive SE with coma</td>
<td>6 (7.5)</td>
</tr>
<tr>
<td>Non-convulsive SE without coma</td>
<td>2 (2.5)</td>
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<td><strong>Etiology according to the 2015 ILAE classification</strong></td>
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<tr>
<td>Acute</td>
<td>86 (84.3)</td>
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<tr>
<td>Infection</td>
<td>79 (91.9)</td>
</tr>
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<td>Intracranial hemorrhage</td>
<td>2 (2.3)</td>
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<td>Anoxia/hypoxia</td>
<td>2 (2.3)</td>
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<tr>
<td>Drug intoxication</td>
<td>1 (1.2)</td>
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<tr>
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<tr>
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<td>Progressive</td>
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<td>Electroclinical syndromes</td>
<td>7 (6.9)</td>
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<td>Dravet syndrome</td>
<td>3 (42.9)</td>
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<td>Epilepsy with myoclonic absence</td>
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<td>Panayiotopoulos syndrome</td>
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</tr>
<tr>
<td>Unknown cause</td>
<td>8 (7.8)</td>
</tr>
</tbody>
</table>

ILAE, International League Against Epilepsy; SE, status epilepticus.

aMicrocephaly (4), Cornelia de Lange-like syndrome (1);
bChoroid plexus tumors (2), meningoima (1); cLeukoencephalopathy with vanishing white matter (2); dMetachromatic leukodystrophy (1), biotinidase deficiency (1);
eAcute disseminated encephalomyelitis (2); fMitochondrial complex II, IV, and V deficiency (1); gNeonatal stroke (1); hPolymicrogyria (1); iCortamazepine intoxication (1); jHypotemia (1); kIntracranial tumor (1); lInfection as possible trigger (4); mdiscontinuation of antiseizure medication as possible trigger (3).
statistically significant (P = 0.065). More than two boluses of BZD were administered in five cases (5/99; 5%).

The preferred second-line ASMs were phenytoin in 67 cases (65.7%) and propofol in eight cases (7.8%). The preferred third-line ASMs were a continuous infusion of midazolam in 24 cases (23.5%) and bolus of phenobarbital in 19 cases (18.6%). The mean number of ASMs used to terminate SE was 3.8 ± 1.1. Midazolam was the ASM most frequently responsible for the termination of SE when given in continuous infusion (47%), followed by propofol (13.7%). Episodes of SE were classified as refractory in 81 cases (79.4%). The duration of SE was 5 to 30 minutes in six cases (6.2%), 30 to 60 minutes in 73 cases (75.3%), and more than 60 minutes in 18 cases (18.6%). In five patients (4.9%), the duration of SE was not recorded. Prolonged episodes (lasting more than 60 minutes) were significantly more frequent in patients with a diagnosis of epilepsy (P = 0.036) and in patients with focal motor SE (P < 0.001) and NCSE (P = 0.037) (Table 2). In-hospital mortality rate was 2.9%.

**Discussion**

To our knowledge, the present study is the first observational study in Portugal that summarizes the epidemiological and clinical characteristics of SE in a pediatric cohort while applying the most recent ILAE guidelines. It represents the real-life decisions of general pediatricians and pediatric intensivists in the difficult management of pediatric SE during the past 11 years. Furthermore, our results are not limited to common practices in our hospital, since we also reviewed data from many patients in whom treatment was initiated before admission or who were transferred from other national health institutions. Most of our findings are in accord with the current literature.

Concerning demographic features, previous studies reported a higher prevalence of SE in boys and preschool children, with median ages ranging from 1.9 to 4.5 years, similar to our results (median age, 2.5 years; IQR, 1.3 to 5.0) [1,5,11-13].

In clinical aspects such as etiology and semiology, we also obtained some expected findings, which were more easily compared to the existing literature due to the standardization provided by the 2015 ILAE guidelines. According to several papers, acute symptomatic etiology is the most common cause of pediatric SE [1,11,14]. Unlike a study performed by Chiarello et al. [5] in a unit with primarily hematological-oncological disorders, our data set included only three patients with a personal history of brain tumor, even though our hospital is a regional referral center, and only one patient displayed an episode of SE on account of progressive etiology. This may be due to two factors: prophylactic ASM and early treatment were given to patients with brain tumors, which stopped seizures from evolving to SE, and some patients with brain tumors and SE could have lacked a discharge ICD-10 code for SE and therefore were missed in our research.

The prevalence of unknown (cryptogenic) etiology has mixed results in the literature, which may be due to the characteristics of the populations studied, namely the percentage of patients with a

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=97)</th>
<th>Episodes of SE &gt;60 minutes (n=18)</th>
<th>Episodes of SE ≤60 minutes (n=79)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>52 (53.6)</td>
<td>9 (50)</td>
<td>43 (54.4)</td>
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<tr>
<td>Age &lt;2 years</td>
<td>41 (42.3)</td>
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<td>Epilepsy</td>
<td>47 (48.5)</td>
<td>13 (72.2)</td>
<td>34 (43)</td>
<td>0.025*</td>
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<td>Additional neurological disorders</td>
<td>16 (16.5)</td>
<td>4 (22.2)</td>
<td>12 (15.2)</td>
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<tr>
<td>Semiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With prominent motor features</td>
<td>89 (91.8)</td>
<td>14 (77.8)</td>
<td>75 (94.9)</td>
<td>0.037*</td>
</tr>
<tr>
<td>Convulsive SE</td>
<td>71 (79.8)</td>
<td>3 (21.4)</td>
<td>68 (89.7)</td>
<td>&lt;0.001*</td>
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<tr>
<td>Focal motor</td>
<td>16 (18)</td>
<td>11 (78.6)</td>
<td>5 (6.7)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Tonic status</td>
<td>2 (2.2)</td>
<td>0</td>
<td>2 (2.7)</td>
<td>&gt;0.999*</td>
</tr>
<tr>
<td>Without prominent motor features (NCSE)</td>
<td>8 (8.2)</td>
<td>4 (22.2)</td>
<td>4 (5.1)</td>
<td>0.037*</td>
</tr>
<tr>
<td>With coma</td>
<td>6 (7.5)</td>
<td>4 (100)</td>
<td>2 (50)</td>
<td>0.429*</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
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<td></td>
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<tr>
<td>Acute</td>
<td>83 (85.6)</td>
<td>14 (77.8)</td>
<td>69 (87.3)</td>
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<tr>
<td>Progressive</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (1.3)</td>
<td>&gt;0.999*</td>
</tr>
<tr>
<td>Electroclinical syndromes</td>
<td>5 (5.2)</td>
<td>2 (11.1)</td>
<td>3 (3.8)</td>
<td>0.231*</td>
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<tr>
<td>Unknown</td>
<td>8 (8.2)</td>
<td>2 (11.1)</td>
<td>6 (7.6)</td>
<td>0.429*</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

SE, status epilepticus; NCSE, non-convulsive status epilepticus.

*Chi-square test; †Fisher exact test.

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previous diagnosis of epilepsy. Interestingly, some researchers have noticed that unknown causes of SE were more prevalent in children older than 2 years, which we also verified [5,15]. The association between etiology and age was detailed by Shinnar et al. [15], who documented significant differences in the distribution of causes between the first and second year of life, with a rapid decrease in the frequency of acute symptomatic cases and a higher proportion of cryptogenic and remote symptomatic cases in the older children.

CSE, particularly the generalized subtype, was the most frequent semiological classification, which also agrees with many published works [1,5,12,16]. Nonetheless, recent studies have focused on NCSE, especially in the PICU. NCSE is the result of a prolonged electrographic seizure leading to non-convulsive clinical symptoms [5]. In the literature, it accounts for only 6% of the cases, but diagnosis requires a high index of suspicion, since cognitive or behavioral changes are often difficult to notice [1]. In the present study, we were able to confirm the diagnosis of NCSE in 7.8% of our patients, and it was associated with prolonged SE (>60 minutes). Focal motor SE was also associated with episodes >60 minutes. These findings reinforce the importance of semiology and its standardization in pediatric SE.

Rectal diazepam was the preferred first-line BZD, both before arrival at the hospital and at the hospital. Some studies performed in pediatric cohorts have not shown the superiority of any BZD [14]. In a Cochrane review, intravenous lorazepam and intravenous diazepam led to more rapid seizure cessation, but in the absence of intravenous access, buccal midazolam or rectal diazepam were considered acceptable first-line ASMs [17]. Although phenytoin was the most frequently selected second-line ASM, as in previously published studies [12], it was followed by propofol as the second most used. Although propofol is not usually selected as a second-line ASM because of its safety profile, it is very effective in seizure cessation, particularly in refractory cases, and it can be used in the emergency room, especially with support from the PICU team [8]. Midazolam in continuous infusion was the preferred third-line ASM and was most frequently responsible for the termination of SE, as has also been reported in the literature [4].

Despite the recognition of the need for urgent ASM administration, the timing of drug administration remains a significant barrier in pediatric SE. The 2015 ILAE guidelines indicate that the minimum time for starting emergency treatment of SE is 5 minutes for CSE [3]. In our study, the timing of the start of ASM was rarely listed in the clinical records. From the available data, we obtained a median interval of 17.5 minutes between the beginning of SE and ASM in CSE, which is longer than the recommended timing. The circumstances of the occurrence of SE, such as the place of the event (particularly in new-onset SE without at home rescue diazepam), may interfere with the urgent administration of an ASM, and studies on this topic should systematically review this issue.

The longer SE goes untreated, the more likely it is to become BZD-resistant and require anesthetic doses for cessation (refractory SE) [4]. In animal models, this seems to be associated with uptake/decreased surface expression of the BZD-specific gamma-aminobutyric acid receptor subunit γ2 [4]. Refractory SE occurs in 29% to 43% of SE cases, according to the literature [6]. In our study, we found a very high percentage of refractory SE (79.4%). A more recent standardized protocol for the management of pediatric SE has been available in our hospital since 2019, and it suggests using midazolam or diazepam as first-line drugs (the administration routes differ between prehospital or hospital initiation of treatment); levetiracetam, valproate sodium, phenytoin, or phenobarbital as second-line drugs; and midazolam, thiopental, or propofol in continuous intravenous infusion as third-line drugs. It would be interesting to compare the therapeutic management of SE and outcomes in our hospital before and after the implementation of this protocol. In fact, we suspect that some changes in choices of ASM may have occurred after protocol implementation, such as levetiracetam replacing phenytoin as the preferred second-line drug. However, we should note that very prolonged SE (>60 minutes) was significantly associated with a diagnosis of epilepsy. It is known that patients with more severe epilepsy may not respond as well to the standard dosing/dose sequence of ASMs [18]. This raises a question regarding whether management is inappropriately homogeneous when protocols are applied, as has been discussed in previous studies [18].

The main limitation of this study is its retrospective and mainly descriptive nature. Patients were identified based on ICD-10 codes and confirmed by a clinical review; therefore, diagnoses could have been missed. ICD-10 codes are recorded by pediatricians at discharge, and sometimes the cause of SE is coded as the final diagnosis (e.g., infection) and the associated diagnoses are omitted. Intensive care pediatricians may be more likely to systematically codify SE compared to general pediatricians in the ED, which might explain why we obtained a higher proportion of cases admitted in the PICU than we expected. For that reason, refractory cases may have been overestimated, but we also received many patients transferred from other hospitals, which are usually more severe cases. Temporal variables may lack accuracy due to post-management documentation in electronic records by medical doctors. Our results may have been influenced by treatment prior to admission, and we lacked information on the timing of ambulance arrival, duration of transport, and other prehospital data. Semiology was analyzed...
based on medical descriptions, which may have been influenced by experience. We did not obtain complete information about EEG in seizure monitoring, only for diagnostic purposes in NCSE. It would be interesting to evaluate EEG patterns in future studies to better characterize NCSE. Outcomes were not fully explored in this article. The observed in-hospital mortality rate was consistent with mortality rates reported in pediatric cohorts in developed countries [7]; however, neurodevelopmental outcomes were not reviewed, which could be particularly important given the high percentage of prolonged SE in our sample.

In summary, most of our findings are in accord with the current literature, including the most frequent demographic features (boys and preschool children), etiological and semiological classification (acute symptomatic etiology and CSE), and the selection of ASMs (the preferred ASMs were rectal diazepam as first BZD, phenytoin as second-line therapy, and midazolam with a continuous infusion as third-line treatment). The standardization provided by the 2015 ILAE guidelines allowed an easier comparison with other recent studies. Epilepsy, NCSE, and focal motor SE were associated with prolonged SE (>60 minutes), which reinforces the importance of the underlying neurological diseases and semiological standardization in pediatric SE.

This paper reports high percentages of patients with refractory SE. A standardized protocol for the management of pediatric SE has been available in our hospital since 2019, and hopefully, it will allow a more rapid recognition and initial treatment.

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

Author contribution
Conceptualization: AR. Data curation: MJS and TCM. Formal analysis: CGM, RR, and AR. Methodology: CGM and RR. Writing - original draft: CGM. Writing - review & editing: MJS, TCM, RR, and AR.

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References


Clinical Findings of Sydenham Chorea in Pediatric Patients: A Single-Center Retrospective Study

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**Purpose:** Sydenham chorea is known for its rapid, irregular, and aimless involuntary movements and is considered a benign and self-limiting condition among the major manifestations of rheumatic fever. The current study reviewed the demographic, clinical, and paraclinical findings of pediatric patients with Sydenham chorea.

**Methods:** This cross-sectional study was conducted among 22 patients with Sydenham chorea who were admitted to the pediatric wards of Mashhad Imam Reza and Ghaem Hospitals between 2006 and 2016. Data from these patients’ medical records were extracted, organized using checklist forms, and analyzed.

**Results:** Eight patients were male and 14 were female. The average age was 10.09 ± 3.53 years. In 31.8% of patients, chorea was the only sign of rheumatic fever. Chorea was unilateral in 21.1% of patients. The most common clinical findings were, in descending order, jerky movements, facial grimacing, gait disorders, mental disorders, speech disorders, muscle weakness, and milkmaid’s grip. Cardiac auscultation was normal in 76.2% of patients, while a holosystolic murmur was heard in 23.8%. In laboratory exams, 50% of patients were erythrocyte sedimentation rate (ESR)-positive, 31.2% were C-reactive protein (CRP)-positive, and 53.3% were anti-streptolysin O (ASO)-positive. Echocardiography showed the prevalence of mitral regurgitation (63.6%), aortic regurgitation (45.5%), tricuspid regurgitation (22.7%), pulmonary regurgitation (4.5%), and pericardial effusion (4.5%).

**Conclusion:** This study showed that Sydenham chorea can be the only sign of rheumatic fever. This disease typically occurs in children between the ages of 7 and 12. ESR, CRP, and ASO can be the most effective laboratory tests for diagnosis.

**Keywords:** Rheumatic fever; Streptococcus; Chorea

**Introduction**

Rheumatic fever (RF) is among the complications that may develop from group A beta-hemolytic streptococcal (GABHS) infections, resulting from an autoimmune reaction\([1]\). This systemic autoimmune disease is a delayed result of infection with GABHS...
bacteria in the throat area, and most commonly occurs in children between the ages of 5 and 14 years [2,3]. Sydenham chorea is known for its rapid, irregular, and aimless involuntary movements—typically in the face, hands, and feet of the patients—and is considered a benign and self-limiting condition among the major manifestations of RF. Sydenham chorea, which occurs in 20% to 30% of children with RF, is considered a neurological manifestation of RF that shows itself approximately 6 months after the severe infection; however, it can also rarely be an initial sign of RF onset [2,4,5].

Chorea is identified based on its aimless, involuntary movements, muscle weakness and discordance, and mental disorders. These symptoms worsen when the patient is awake or under stress, and disappear during sleep. The entire body is affected, but it is more severe on the face and extremities. Speech may be affected and become explosive or pausing. Patients’ handwriting may be impaired, wavy, or spiky. Arm extension overhead may cause pronation in one or both hands. Irregular hand muscle contractions occur when the patient squeezes the examiner’s hand, and when the patient moves the hands forward, the fingers become hyperextended. The discoordination can easily be observed when a patient is asked to button or unbutton a shirt. Mental instability is clearly visible; there is a tendency toward irritability, stubbornness, and resentment. A child’s teacher may declare that the student is not focused, is anxious, negligible, and does not collaborate [6,7].

Sydenham chorea can be the only sign of RF and thus is sufficient, on its own, to diagnose RF. The diagnosis of Sydenham chorea’s is entirely clinical, based on chorea’s clinical signs, a history of RF, and excluding other causes [8,9]. Poverty, crowded communities, national country population, lack of access to high-quality public health, and fear of physicians prescribing penicillin due to allergic reactions are among the major factors associated with this disease’s prevalence [6,10].

M-type streptococcal serotypes have been more frequently isolated than other streptococcal serotypes in patients with a history of RF; however, since the serotypes are unknown in clinical diagnosis of streptococcal pharyngitis, all group A serotypes need to be considered pathogenic and all infections effectively treated [7]. It is worth noting that not all rheumatogenic serotypes of group A streptococci are equally dangerous [11].

Common antibodies against group A hemolytic streptococci and caudate nucleus neurons are found in patients with Sydenham chorea. These antibodies, also known as anti-basal ganglia antibodies, cause disruptions in basal ganglia neurons. Central nervous system (CNS) vasculitis causes cell degeneration and results in edema in the endothelium of blood vessels, perivascular infiltration, and cerebral petechial hemorrhage [12-14]. In one study, disrupted cerebral circulation was stated as a cause of Sydenham chorea [15].

Genetics plays a critical role in the pathogenesis of Sydenham chorea. For instance, patients with Sydenham chorea have a higher frequency of D8/17 allantogen expression. However, susceptibility to the disease is considered to be an interplay between genetic factors such as this and environmental ones [16].

Despite the low prevalence of RF in developed nations, it is still considered a major problem among children and teenagers in developing countries. Economic impacts caused by disabilities, neurological or mental disorders, or mortality due to RF lead to increased public health costs at regional and national levels. The results of this study can be used to better understand the damages caused by the disease and may change our operational perspective on the matter. Employing clinical and paraclinical findings of the disease would be helpful in early diagnosis, effective treatment of the patients, and prevention of its devastating impacts and increased public health costs.

Materials and Methods

All patients with Sydenham chorea admitted to the pediatric wards of Mashhad Imam Reza and Ghaem Hospitals between 2006 and 2016 were included. This study was conducted with a retrospective approach using patients’ medical records. Data were extracted from the files on age, sex, initial complaint, clinical signs of RF (arthritis, carditis, subcutaneous nodule [SCN], erythema marginatum [ERM], and chorea), clinical signs of Sydenham chorea (walking disorder, pronator sign, muscular weakness, speech issues, lingual dyskinesia, facial grimacing, and mental signs), physical examination including cardiac auscultation, and laboratory results, as well as electrocardiography (ECG), electroencephalography (EEG), echocardiography, and brain magnetic resonance imaging (MRI) results. In cases where the patient information was incomplete (nine patients), additional information was obtained via telephone contact. The data were organized using checklist forms and then analyzed. In this study, the normal limits for the erythrocyte sedimentation rate (ESR) and anti-streptolysin O (ASO) were defined as 20 mm/hr and 200 IU/mL, respectively. Leukocytosis was defined as white blood cell (WBC) count > 11,000/mm³, leukopenia as WBC count < 3,700/mm³, thrombocytosis as platelet count > 500,000 µL, and anemia as hemoglobin < 11 and < 12 g/dL in children aged 5 years and under and children older than 5 years, respectively.

Fever was defined as an oral temperature ≥37.8°C. The normal value for the ejection fraction was defined as being between 56% and 78%. Carditis was defined as a new pathological valvular lesion...
detected via echocardiography.

This study was approved by the medical ethics committee of Mashhad University of Medical Sciences (Ethics code: IR.MUMS.fm.REC.1396.722). All patients and their families were informed and signed consent forms. The information used in this study was gathered from an anonymized data bank, and thus no personal information on patients’ identities has been revealed.

After completion of the checklist forms, the data were entered into SPSS version 10 (SPSS Inc., Chicago, IL, USA) and analyzed. The results were described in the form of tables, figures, and central and dispersion indexes.

The normality of the data distribution was checked using the Kolmogorov-Smirnov test. The t-test and Mann-Whitney U test were conducted in order to identify the relationships among quantitative variables for data with normal and non-normal distributions, respectively. The relationships among qualitative variables were determined using the chi-square and Fisher exact tests. Correlations were also examined using the Pearson test for normally distributed data and the Spearman test for non-normally distributed data. The statistical analysis was conducted using SPSS version 10 (SPSS Inc., Chicago, IL, USA), and a P<0.05 was considered to indicate statistical significance.

Patient and public involvement

Neither patients nor the public was involved in the design, implementation, reporting, or dissemination plans of this study.

Results

This study was conducted on 22 patients. The diagnoses of Sydenham chorea were made by pediatric neurologists based on clinical symptoms, history of RF, and the exclusion of other causes of chorea. Studied cases included eight boys (36.4%) and 14 girls (63.6%), with an average age of 10.09 ± 3.53 years (range, 3 to 17).

Fig. 1 illustrates the age distribution of patients included in this study.

The average weight of the patients at birth was 2.83±0.67 kg, and the average weight upon hospital admission was 30.29±10.93 kg. Seventeen patients (77.3%) were born vaginally, while five were born by cesarean section (22.7%). Among 22 patients, 20 were born full-term, one was born pre-term, and one was born post-term. Nine patients were the family’s first child, seven patients were the second child, four patients were the third child, and two patients were the fourth child. Nine of the parents were relatives (cousins), and 13 were unrelated.

The reasons for referral to the hospital were chorea for 19 patients (86.4%), fever for two patients (9.1%), and arthritis for one patient (4.5%). In 31.8% of patients, chorea was the only sign of RF. Fifteen patients manifested both chorea and carditis, while no patients manifested arthritis, ERM, or SCN. Two of the studied patients had a history of arthritis (10 to 14 days prior to the onset of chorea), and one patient had a history of ERM (2 weeks before chorea). Chorea was bilateral in 78.9% of patients and unilateral in 21.1% of patients.

A study of the patients’ clinical findings showed the following significant signs of Sydenham chorea, in descending order of frequency: jerky movements (86.4%), facial grimacing (59%), gait disorders (59%), mental disorders (47.4%), speech problems (47.4%), muscle weakness (42.1%), milkmaid’s grip (42.1%), lingual dyskinesia (26.3%), fever (22.7%), the pronator sign (21.1%), and the Babinski sign (9%). Fig. 2 shows the distribution of patients based on determined clinical findings.

Cardiac auscultation detected a holosystolic murmur in 23.8%
of patients, while 76.2% had normal results. In laboratory examinations, 50% of patients were ESR-positive, 32.2% were C-reactive protein-positive, and 53.3% were ASO-positive, with an average ASO value of 296.67±342.50 IU/mL. Throat cultures obtained from four patients all showed negative results. Complete blood count (CBC) tests for 15 patients showed that none of the patients had leukopenia, while 13.3% had leukocytosis, 33.3% had anemia, and 13.3% had thrombocytosis.

ECG and MRI examinations conducted on the patients did not result in any pathological findings, while EEG showed nonspecific epileptic discharges in one patient. Echocardiography detected cardiac rheumatism in 14 of the patients; all 14 had mitral valve regurgitation. The most common type of accompanying cardiac valve involvement was mitral and aortic valve regurgitation (71.42%), followed in descending order by mitral valve regurgitation (63.6%), aortic valve regurgitation (45.5%), tricuspid valve regurgitation (22.7%), pulmonary valve regurgitation (4.5%), and pericardial effusion (4.5%). Left ventricular function and right ventricular function in all 22 patients were normal. Fig. 3 shows the patient distribution based on cardiac valve involvement.

Table 1 lists the relationship between the study variables and the patients’ sex. Of eight male patients, all had carditis, while only seven out of 14 female patients had carditis. Carditis was significantly more common in boys than in girls ($P<0.05$). Furthermore, in patients’ clinical findings, two boys and 11 girls had facial grimacing. Facial grimacing was significantly more common in girls than in boys ($P<0.05$). There was no meaningful correlation between patients’ sex and other variables ($P>0.05$).

Table 2 shows the relationships between cardiac auscultation and echocardiography findings of the patients. There was no meaningful correlation between the cardiac auscultation and echocardiography results ($P>0.05$).

Reviewing the statistical indicators of the relationship between hearing a heart murmur and diagnosing carditis on echocardiography, murmur showed a sensitivity of 30.77%, specificity of 87.50%, positive predictive value of 80%, and negative predictive value of 43.75%.

None of the 22 patients had any associated anomalies. In the 1- to 10-year follow-up, none experienced a recurrence of chorea, and one died due to heart problems.

**Discussion**

The current study aimed to review demographic, clinical, and paraclinical findings on pediatric patients with Sydenham chorea. This study showed that Sydenham chorea can be the only sign of RF and is significant in diagnosing the disease alongside the clinical symptoms. As discussed, the most common symptoms of Sydenham chorea are, in order of diminishing frequency, jerky movements, facial grimacing, gait disorders, mental disorders, speech disorders, muscle weakness, milkmaid’s grip, lingual dyskinesia, fever, pronator sign, and Babinski sign. The disease is most common among children between the ages of 7 and 12 years, but may still be seen in other age groups.

Study findings showed more prevalence of Sydenham chorea among girls than among men, and the average age of the patients was 10.09 years. Carditis was more common in men, while the prevalence of facial grimacing was more common in women. However, we believe that, due to the limited number of patient cases, further studies with larger sample sizes are needed in order to be able to interpret the divergent frequencies of carditis and facial grimacing between boys and women.

In 31.8% of patients, chorea was the only sign of RF, while in 68.2%, other major signs were observed, the most common of which was carditis. None of the patients had concurrent arthritis, ERM, or SCN with chorea, which can be due to the fact that major symptoms other than carditis disappear earlier, while carditis and chorea are the two delayed signs. In our study, laboratory tests were positive for ESR, CRP, and ASO in 50%, 31.2%, and 53.3% of the patients, respectively. Throat culture results were negative for all four patients undergoing the test. We believe that throat cultures are usually negative by the time chorea appears, as chorea is a delayed complication of RF.

The most common laboratory findings in patients’ CBCs were anemia, leukocytosis, and thrombocytosis. The patients’ neuroimaging histories were reviewed, and patients’ brain MRIs were all normal. No correlation was observed between the cardiac auscultation and echocardiography findings. Despite the normal results of cardiac auscultation in patients, echocardiography showed 63.6% of them with rheumatic heart disease. The most common
### Table 1. Correlations of the study variables with sex

<table>
<thead>
<tr>
<th>Variable</th>
<th>Division</th>
<th>Male</th>
<th>Female</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
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<td>1</td>
<td>0.716</td>
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<tr>
<td></td>
<td>Negative</td>
<td>7</td>
<td>12</td>
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<tr>
<td>Carditis</td>
<td>Positive</td>
<td>8</td>
<td>7</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>0</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>SCN</td>
<td>Positive</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>8</td>
<td>13</td>
<td></td>
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<tr>
<td>ERM</td>
<td>Positive</td>
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</tr>
<tr>
<td></td>
<td>Negative</td>
<td>8</td>
<td>12</td>
<td></td>
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<tr>
<td>Jerky movements</td>
<td>Positive</td>
<td>6</td>
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<tr>
<td></td>
<td>Negative</td>
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<td>1</td>
<td></td>
</tr>
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<td>Gait disorder</td>
<td>Positive</td>
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<td>7</td>
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<tr>
<td></td>
<td>Negative</td>
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<td>6</td>
<td></td>
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<tr>
<td>Milkmaid’s grip</td>
<td>Positive</td>
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<tr>
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SCN, subcutaneous nodule; ERM, erythema marginatum; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ASO, anti-streptolysin O; MRI, magnetic resonance imaging; EEG, electroencephalography; ECG, electrocardiography; MR, mitral regurgitation; AR, atrial regurgitation; TR, tricuspid regurgitation; PR, pulmonary valve regurgitation.

Sydenham chorea is a rare sign of acute rheumatic fever (ARF), which is shown by a few patients and can be the only sign. The inflammation process in the CNS involves basal ganglia and caudate nucleus neurons. While the incubation period from the onset of streptococcal pharyngitis until carditis and arthritis symptoms is 3 weeks on average, it is 3 months or longer for Sydenham chorea [1,17]. Most patients with Sydenham chorea are treated and recover within 6 months (typically in 6 weeks); however, there have been cases observed in which the disease persists for 3 years [18]. MRI scans are typically normal, and positron emission tomography scans show elevated levels of metabolism in the striatum. Neurochemical studies have reported reductions in gamma-aminobutyric acid in basal ganglia cells [12,19-23].

There is no specific test to diagnose Sydenham chorea and ARF. The diagnosis of RF is made using the Jones criteria [24]. ARF is diagnosed based on clinical findings and strong clinical suspicion, especially considering that there is no history of acute streptococcal pharyngitis in one-third of the cases [6,10,11]. Chew et al. [25] reviewed the prevalence, epidemiology, and clinical signs of Sydenham chorea and showed an average age of 11.5 years among 37 patients, with most patients (68%) under 12 years old.
years old, and a female-to-male ratio of 1.01 to 1. Two-thirds of patients had bilateral chorea, and one-third had unilateral chorea. The most common neurological clinical signs of the patients reported were, in descending frequency, facial grimacing (38%), dysarthria (25%), and gait disorders (21%), with no patients showing signs of seizure. While chorea was the only clinical sign in 65% of the patients, some patients showed other signs of RF as well, including carditis (35%), arthralgia (24%), fever (2%), SCN (11%), arthritis (5%), and ERM (3%) [25].

In a research study conducted by Regmi et al. [26], 16 patients with chorea had carditis, six patients had arthritis, and only four patients had chorea as the only sign of RF. In a study by Ekici et al. [27], the most common clinical signs were behavioral changes and muscle weakness. Tumas et al. [28] reported the most common clinical findings among pediatric patients to be behavioral disorders (40%), dysarthria (39%), and gait disorders (34%). However, in our study, we reported the most common signs to be, in descending order of frequency, jerky movements, facial grimacing, gait disorders, mental disorders, speech problems, muscle weakness, milkmaid’s grip, dyskinesia, fever, the pronator sign, and the Babinski sign, with bilateral and unilateral chorea in 78.9% and 21.1% of the patients, respectively. In our study, in 31.8% of the patients, chorea was the only sign of RF, while 68.2% had chorea with other major signs of RF. Two patients had a history of arthritis, and one had a history of ERM. Fifteen patients had carditis, while no SCN was found in any patients.

In the study by Chew et al. [25], EEG showed abnormal findings in four patients, while patients’ brain computed tomography scans showed no pathologic findings. In the of Ekici et al. [27], brain MRI showed abnormal nonspecific findings in 47% of the patients with hyper-signal intensities in white matter, brainstem, and caudate nucleus. In our study, no pathological findings were observed in the patients’ brain MRI scans, and EEG also showed nonspecific epileptic discharges in one patient.

In the study by Gurkas et al. [29], recurrence was documented in 16% of patients during 6 months to 9 years of follow-up. In contrast, no patients experienced disease recurrence in the study of Kilic et al. [22] In our study, a 1- to 10-year follow-up showed no recurrence of the disease in the studied patients, of whom only one died due to heart problems.

In conclusion, any child showing symptoms of Sydenham chorea needs to be examined by a physician and, if deemed necessary, undergo further examination or tests. Early treatment would prevent further complications and typically results in full recovery.

This study showed that, among laboratory results, ESR, CRP, and ASO typically show elevated levels in Sydenham chorea patients, which can be helpful for diagnosis. These laboratory results can be employed to diagnose this disease more purposefully despite the lack of any relationship between them and the clinical findings. However, it should be mentioned that laboratory tests such as ESR, CRP, and ASO might be negative, and their negativity might be explained by the interval between the acute bacterial infection and the occurrence of Sydenham’s chorea.

Although holosystolic murmur was only observed in 23.8% of the patients on cardiac auscultation, 63% of the patients showed cardiac rheumatism on echocardiography. These results show the importance of strong clinical suspicion in diagnosing cardiac rheumatism and other cardiac issues by echocardiography.

Further studies are recommended to be conducted at multiple centers and with a higher number of patients in order to obtain a more comprehensive clinical perspective of this disease using statistical methods.

### Conflicts of interest

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

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Author contribution

Conceptualization: HMMS. Data curation: HMMS, EH, MBT, and AM. Formal analysis: AP. Methodology: AP. Project administration: HMMS. Visualization: HMMS, MBT, and AM. Writing-original draft: HMMS, EH, and AP. Writing-review & editing: HMMS, EH, and AP.

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References


Assessment of Sleep Disorders in Children with Transfusion–Dependent Hemoglobinopathies

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**Purpose:** The aim of this study was to compare sleep problems between children with transfusion–dependent hemoglobinopathies and healthy controls.

**Methods:** This study was a case-control survey of children with transfusion–dependent hemoglobinopathies. The sample consisted of 175 children in the patient group and 175 healthy children in the control group, with an age range of 8 to 18 years. Subjects were recruited from the Children’s Hospital of Mansoura University between February and July 2022. Children with transfusion-dependent hemoglobinopathies received consultations at the Department of Pediatric Hematology. The Children’s Sleep Habits Questionnaire (CSHQ) was used to evaluate sleep problems in both groups.

**Results:** The mean age of the patient group was 11.22±2.39 years, and 52.57% (n=92) were girls. The control group had a mean age of 11.30±2.16 years, and 50.86% (n=89) were boys. The overall score (P=0.007) and the night waking (P=0.013), sleep duration (P=0.009), and sleep-disordered breathing (P=0.029) subscores were all substantially and statistically significantly higher in children with transfusion–dependent hemoglobinopathies than in healthy children.

**Conclusion:** As children with transfusion–dependent hemoglobinopathies have more sleep problems than healthy children, more detailed studies are needed.

**Keywords:** Hemoglobinopathies; Sleep wake disorders; Thalassemia; Anemia, sickle cell

**Introduction**

Hereditary hemoglobin diseases, often known as hemoglobinopathies, are a set of hereditary illnesses involving the structure of hemoglobin. Sickle cell disease (SCD) and thalassemias constitute the majority of these conditions \([1,2]\). These illnesses are among the most prevalent inherited conditions in the world; the birth rate of individuals who are homozygous or compound heterozygous for symptomatic hemoglobin disorders is around 2.4 per 1,000 births, of whom 1.96 have SCD and 0.44 have thalassemia \([3,4]\).

A β-globin gene mutation produces sickle hemoglobin, which fills red blood cells and changes their shape and flexibility (the "sickling" process). Exercise and oxidative stress enhance cellular dehydration. Hemoglobin deoxygenation and the intracellular sickle cell hemoglobin concentration affect sickling, polymerization, and severity \([5,6]\). A vaso-occlusive or hemolytic pathophysiology generates acute and persistent SCD symptoms \([7,8]\). Vaso-occlusive disease causes chest discomfort and osteonecrosis,
Sleep is one of the essential daily requirements for humans. Sleep promotes cellular regeneration, relaxation, comfort, and physical-mental rest. Numerous studies have shown that sleep disturbances are particularly common in sick people [20]. Children with chronic illnesses are affected by a variety of physical and behavioral issues, including sleep disturbances. Chronic illnesses are a leading cause of disability and death. Studies have shown that 30% to 75% of newly diagnosed cancer patients experience a range of sleep difficulties [21]. These patients’ sleep disturbances result in chronic weariness, decreased adherence to therapy, and a diminished quality of life [22]. Only 17% of people with a sleep disturbance are checked and treated by doctors, despite the significance of sleep quality [23]. Transfusion-dependent hemoglobinopathies cause various psychological and physical difficulties in sufferers. In particular, these patients often experience a high degree of worry, which disrupts their sleep [24]. However, little research has been undertaken on this topic [25].

Sleep-related disorders are sleep-pattern-altering abnormalities that result in inadequate or poor-quality sleep. Sleep-disordered breathing (e.g., OSA and upper airway obstruction), restless legs syndrome, and insomnia are sleep disorders that make it difficult to begin or sustain high-quality sleep [26]. In the general pediatric population, sleep difficulties are linked with poor effects on learning and attention, diminished cognition, behavioral issues, and reduced health-related quality of life [21].

Considering the high prevalence of snoring and other sleep problems in children with transfusion-dependent hemoglobinopathies and given the time constraints of busy pediatricians to screen for sleep disorders, screening tools have been developed to assist pediatricians in recognizing these symptoms [27]. These questionnaires are comprehensive and are capable of predicting the probability of sleep disorders with a relatively high degree of accuracy [28].

A polysomnographic study (PSG) is the diagnostic technique of choice for quantifying sleep-disordered breathing and sleep architecture. PSG can be performed in children of all ages [29]. PSG is not only useful for diagnosis, but also allows the severity of the disease to be estimated, despite certain limitations: PSG is intrusive, cumbersome, and cost-prohibitive, and facilities that can provide PSG-based diagnostic services in children are not widely available. Furthermore, normative values are based on the statistical distribution of data, and to date, abnormal PSG variables seen in children with OSA have failed to predict adverse clinical outcomes [30].

Given the limitations of PSG, several screening studies have been suggested as a means to distinguish primary snoring and OSA. These studies are based on the frequency and severity of the three cardinal symptoms of sleep apnea: snoring, labored breathing, and oxygen desaturation [31]. Nap studies and overnight oximetry studies have high specificity but low sensitivity; thus, overnight PSG is needed to make the diagnosis in children with negative studies. The other limitations of screening studies include difficulty in estimating the severity of the disease, inability to exclude causes of hypoxemia other than OSA, and an inability to diagnose upper airway resistance syndrome and obstructive hypoventilation, which are other variants of sleep-disordered breathing in children [32].

To the best of our knowledge, existing research on the sleeping...
patterns and behaviors of children and adolescents with transfusion-dependent hemoglobinopathies, which cause chronic hemolytic anemia, is inadequate [33]. This study intended to compare sleep difficulties between children with transfusion-dependent hemoglobinopathies and healthy controls [34].

Materials and Methods

1. Aim of the study
The aim of this study was to compare sleep problems between children with transfusion-dependent hemoglobinopathies and healthy controls.

2. Research design
A case-control design was used in this study.

3. Study subjects
A convenience sample of 175 children with transfusion-dependent hemoglobinopathies who attended the inpatient hematologic department and outpatient hematology clinic of the Children’s Hospital of Mansoura University was selected for this study, and 175 healthy controls completed the study requirements and were included in the study. In total, 405 children, ranging in age from 8 to 18 years, attended the above-mentioned departments during the 6-month period from February 1, 2021 to July 31, 2022. An assessment for hemoglobinopathy often comprises tests that identify the different forms of hemoglobin and quantify their levels. The information obtained from these tests, in conjunction with the outcomes of standard tests such as a complete blood count, a blood smear, and electrophoresis of globin proteins, helps to reach a diagnosis. There are two categories of children who are diagnosed with hemoglobinopathies: those who need regular blood transfusions (transfusion-dependent) and those who do not (non-transfusion-dependent).

The subjects of this study were required to meet the following criteria (Fig. 1):

(1) Age: between 8 and 18 years
(2) Sex: both sexes
(3) Children who visited the outpatient clinic and inpatient department of the Children’s Hospital of Mansoura University.
(4) Children who were transfusion-dependent

The exclusion criteria comprised patients with co-morbid illnesses, such as intellectual disability, endocrinological diseases (e.g., diabetes mellitus), cardiovascular diseases, respiratory problems (e.g., asthma), kidney disease (e.g., renal failure), and neurological disorders (e.g., epilepsy and seizures). For context regarding the subjects' educational level, the public education system in Egypt consists of three levels: the primary educational level for 6 years, starting from 6 to 11 years of age; preparatory school for 3 years, starting from 12 to 14 years of age; and, the secondary school stage for 3 years, from ages 15 to 17 years of age.

4. Data collection tools
Information was collected on children’s sociodemographic characteristics and clinical data using a sheet designed by the researcher based on a review of the literature for the collection of sociodemographic data from children and their caregivers. The variables included (1) sociodemographic data of children (age, sex, birth order, and level of education) and (2) clinical data from children with hematological disorders, such as the onset of the disease, duration of illness, frequency of blood transfusion, the presence of any other disease (e.g., diabetes mellitus, heart disease [cardiomegaly], and bone deformities [fractures or osteoporosis]), and the presence of thalassemia in the family (including the number of brothers or sisters affected by thalassemia and the familial relationship between parents).

The Children’s Sleep Habits Questionnaire (CSHQ) is a 45-item parent survey that has been used in past studies to evaluate how children sleep and determine whether they have any problems [35]. The CSHQ includes items on bedtime resistance (items 1, 3, 4, 5, 6, and 8), sleep onset delay (item 2), sleep duration (items 9, 10, and 11), sleep anxiety (items 5, 7, 8, and 21), night waking (items 16, 24, and 25), sleep-disordered breathing (items 18, 19, and 20), parasomnias (items 12, 13, 14, 15, 17, 22, and 23), and morning waking/daytime sleepiness (items 26, 27, 28, 29, 30, 31, 32, and 33). Items are rated on a 3-point scale: "usually" if the sleep...
behavior occurs five to seven times per week; "sometimes" for two to four times per week; and "rarely" for zero to one time per week. Items 1, 2, 3, 10, 11, and 26 are reverse-coded.

Parents retrospectively complete the CSHQ and are asked to assess the child’s sleep habits over the previous week. It generally takes 5 to 15 minutes to fill out the questionnaire. A total of 41 points has been suggested as a cut-off point, with higher scores considered to be clinically significant. The Arabic version used in the present work was developed through a translation and retranslation process by Asaad and Kahla [36].

5. Statistical analysis
The collected data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Demographic variables were presented using descriptive statistics. Categorical variables were compared using the chi-square test. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to check the normality of data distribution for all continuous variables. Normally distributed parametric variables were compared between groups using the independent-samples t-test. A P value <0.05 was considered to indicate statistical significance.

6. Ethical considerations
Verbal informed consent was obtained from all children and their caregivers. All children and their caregivers were informed of their right to refuse or withdraw at any time. The children’s privacy was maintained. Ethical committee approval was obtained from the Research Ethics Committee of the Faculty of Nursing, Mansoura University (MFN-IRB No. 2022-02-0113).

Results
Table 1 shows the frequency distribution of the children according to their sociodemographic and clinical characteristics. Approximately two-thirds (62.86%) of the children in the patient group were in the age group of 8 years to less than 12 years, with a mean age of 11.22±2.39 years. Likewise, almost two-thirds (60.57%) of the children in the control group were in the age group of 8 years to less than 12 years, with a mean age of 11.30±2.16 years. In addition, girls represented a higher percentage (52.57%) in the patient group than in the control group (50.86%). Almost half of the children were first children in both the patient group (41.14%) and the control group (44.57%). Approximately two-thirds of the children were at the primary level in both the patient group (62.86%) and control group (66.29%). Statistically significant differences were not found between the two groups in terms of age, sex, educational level, or birth order.

Table 2 shows the distribution of patients according to their clinical data. More than half of the patients (51.43%) had beta-thalassemia major and a similar percentage (53.71%) had a blood transfusion rate of once monthly. The mean age of children when the disease was diagnosed was 7.49±3.06 months, which was also children’s mean age of children at the time of the first blood transfusion. More than three-quarters of the studied children (77.71%)

Table 1. Distribution of children according to their sociodemographic and clinical characteristics

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<td>41.14</td>
<td>78</td>
</tr>
<tr>
<td>Second</td>
<td>36</td>
<td>20.57</td>
<td>31</td>
</tr>
<tr>
<td>Third</td>
<td>58</td>
<td>33.14</td>
<td>43</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>5.14</td>
<td>23</td>
</tr>
</tbody>
</table>

SD, standard deviation.
had a related disease that was detected urgently. Most of the children (80.57%) had splenomegaly, the majority (79.43%) had cardiomegaly, approximately three-quarters of the children (71.43%) had hepatomegaly, over four-fifths of the study children (85.14%) had osteoporosis, and approximately three-quarters (76.0%) had a bone deformity.

Table 3 presents a comparison of CSHQ ratings between the patient and control groups. When compared to the control group, the overall score \( (P=0.007) \) and the night waking \( (P=0.013) \), sleep duration \( (P=0.009) \), and sleep-disordered breathing \( (P=0.029) \) subscores were all substantially higher in the patient group. Although the patient group had greater levels of bedtime resistance \( (P=0.091) \), sleep start delay \( (P=0.547) \), sleep anxiety \( (P=0.105) \), daytime sleepiness \( (P=0.711) \), and parasomnias \( (P=0.200) \), these results did not reach statistical significance. Furthermore, higher scores were found for sleep disorders in SCD patients than in patients with thalassemia.

Discussion

In order to address the research gap related to sleep disorders in children with transfusion-dependent hemoglobinopathies, the purpose of the present study was to compare sleep problems between children with transfusion-dependent hemoglobinopathies and healthy controls. According to the comments of the children’s parents on the CSHQ scale, the researchers in this study compared the sleeping patterns and behaviors between these two groups of children.

Several reports have described difficulties sleeping among children and adolescents who have hemoglobinopathies. The majority of these findings are linked to SCD, a hereditary hemoglobinopathy that is characterized by persistent hemolysis and increased extramedullary hematopoiesis similar to that seen in thalassemia. However, relatively little research has investigated the connection between thalassemia and sleep disorders \([37]\).
We identified evidence of disturbed sleep in a clinical sample of children with transfusion-dependent hemoglobinopathies. By all measures, the sleep disturbances in our sample, compared to published samples of healthy children, were severe, in agreement with the findings of other studies. In a study conducted by Tarasiku et al. [38], the authors concluded that children and adolescents with beta-thalassemia or congenital dyserythropoietic anemia type 1 showed impaired sleep function, which was partially related to periodic limb movements and arousals that result in daytime sleepiness. Another study designed by Sritppardawan et al. [39] showed higher prevalence rates of OSA in children with severe beta-thalassemia. Our findings in this study were consistent with the literature. Parents of children with beta-thalassemia major reported more sleep disturbances than those of healthy children. Furthermore, night waking and sleep-disordered breathing were reported to be more common in children with beta-thalassemia major. Reporting these two types of sleep problems together may be an important point, since it may be speculated that sleep-disordered breathing could cause children to wake up more often during the sleep period.

There is a lack of understanding of the mechanism behind sleep disorders in children with beta-thalassemia. Kapelushnik et al. [40] described a child with both OSA and thalassemia intermedia. They hypothesized that the child’s OSA was caused by extramedullary hematopoiesis in the nasopharyngeal region. All of the patients in the study by Sritppardawan et al. [39] who had OSA also had adenoid hypertrophy, and 80% of them also had related tonsil enlargement. All of the lymphoid tissues found in the adenotonsillar region had reactive lymphoid hyperplasia in their investigation, but there was no indication of extramedullary erythropoiesis. The authors hypothesized that lymphoid hyperplasia could be connected to recurrent infections of the adenotonsillar tissue, similar to SCD [41].

The limitations of the current study should be taken into consideration when judging the significance of its findings. The fact that we relied on information from the parents is a significant constraint [41,42]. Their interpretation of the child’s condition can be colored by the difficulties they are experiencing as parents. For instance, depressed parents may have a more pessimistic outlook on their children’s quality of sleep [43]. Both polysomnography and actigraphy are objective measurements that may be used to precisely assess whether or not a child or teenager is experiencing sleep issues [43,44]. Another disadvantage is that no family or environmental factors were considered, such as marital issues, socioeconomic position, or the setting in which the subject slept. There is a possibility that these factors can also affect young children’s sleep quality [41].

In conclusion, transfusion-dependent hemoglobinopathies may increase the risk of sleep disturbances in children and adolescents, particularly those with SCD rather than thalassemia. Hence, assessing children with transfusion-dependent hemoglobinopathies during their routine clinical check-ups is crucial. Disrupted sleep has been linked to poor cognitive and scholastic performance, behavioral difficulties, and symptoms of depression and anxiety [19-21]. Sleep issues may make it harder for children to function, develop, and manage the main symptoms of beta-thalassemia. For patients with this disease, regular clinical evaluations should examine sleep disorders, including insomnia, nocturnal awakening, sleepwalking, sleep apnea, and daytime sleepiness. Managing children’s sleep concerns may also improve therapeutic compliance. Working with parents to improve the sleeping environment may improve sleep quality and quantity (for example, by making the surroundings calmer). Educating parents and children on efficient sleep and bedtime routines at regular healthcare visits may improve children’s sleep efficacy.

Conflicts of interest

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

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Author contribution

Conceptualization: MAE. Data curation: MAE. Formal analysis: AMA. Methodology: AMA and ADM. Project administration: AMA. Visualization: ADM. Writing-original draft: AMA. Writing-review & editing: ADM and MAE.

References


Effectiveness of a Training Program for Parents of Toddlers with or at Risk of Autism Spectrum Disorder

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Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by the lack of social communication skills with limited and repetitive behaviors [1]. In the United States, one in 44 children has been reported to have ASD, and the cost of education and treatment for ASD is estimated to be approximately $2.4 million per person [2,3]. A growing body of research suggests that ini-
tiating interventions focusing on core social deficits as early as possible can greatly improve outcomes for children with ASD [4]. Young children with ASD typically have core deficits in social communication skills, such as sharing affect, making eye contact, shifting gaze from one person to another, using symbolic gestures, and engaging in joint attention [5]. Joint attention refers to nonverbal communicative behaviors of pointing, showing, and sharing interest, and it is regarded as a strong predictor of future language development, social skills, and adaptive functions [6]. Current research on toddlers with ASD emphasizes providing behavioral interventions in a natural environment optimized for development. Schreibman et al. [7] reported that young children with ASD who received naturalistic developmental behavioral interventions (ND-BIs) as state-of-the-art treatment made achievements in cognitive skills, adaptive behaviors, and social communication skills.

Effective early interventions are an important priority for serving children and families; since families are now considered experts on their children, they often participate in implementing roles [8,9]. As children are at an early developmental stage, parent-implemented intervention (PII), an evidence-based practice, is highly recommended in the literature [10]. Recent research has shown that parents raising toddlers with ASD can acquire basic knowledge and implement teaching strategies, acting as interventionists in their toddlers’ daily lives [11,12]. Parents who learned about early development and ASD features were able to plan individualized interventions and successfully implement interventions throughout their daily routines [13,14]. Moreover, the parent-led group showed a significant increase in the length of jointly engaged time compared to the therapist-led group, and this increase was maintained at the 6-month follow-up [5].

Many efforts are being made to advance the timing of early interventions and to provide parents with effective interventions. For example, a university hospital in Hong Kong conducted parent training for 2 weeks while waiting for official services immediately after diagnosis and reported improvements in all areas and reduction of parental stress among toddlers who participated in education programs focused on social communication skills, such as eye contact, gesture, and language [15]. In Quebec, Canada, 94 toddlers with ASD and their parents were examined for 1 year to promote toddler development, and the study reported high parental satisfaction [16]. Stanford University Hospital in the United States provides free parental support programs to help parents raise autistic infants, providing effective links to early intervention services and achieving high parental satisfaction [17]. Florida State University Hospital further supports community early intervention programs [18].

The rapid increase in the incidence of ASD has significantly affected Korean medical and educational sites that support toddlers. Many families of children with early ASD symptoms seek services before a formal diagnosis due to delays in expressive language development and social interaction skills. Despite the recognized importance of early interventions, in Korea, group studies verifying the effectiveness of interventions for toddlers with ASD and their parents are limited [19]. Moreover, Studies that targeted both toddlers with ASD and their parents conducted on related topics over the past 5 years have varied in terms of the age, period, intervention method, and intensity of the programs of the participating toddlers and their parents. Additionally, early interventions or parental support programs provided by the public system for toddlers and parents affected or at risk of ASD are implemented to a very limited extent. Therefore, it is necessary to evaluate the performance of interventions through practical application. Furthermore, after the outbreak of coronavirus disease 2019 (COVID-19), toddlers with ASD and their parents experienced restrictions on the use of special education services, and most face-to-face parental education programs were canceled or conducted intermittently. These issues have prompted a need for alternative methods to increase the individual accessibility of services for parents of children with ASD by merging non-face-to-face methods with existing education programs and reducing the cost and time of direct visits. This study aimed to develop and investigate the effectiveness of a hospital-provided hybrid training program for parents of toddlers with or at risk of ASD.

Materials and Methods

1. Study population

The participants included 24 pairs of toddlers and parents residing in Seoul, Incheon, and Gyeonggi Province, in which the children were diagnosed with or the risk of ASD at the National Health Insurance Service Ilsan Hospital Development Delay Clinic. The inclusion criteria included: (1) toddlers younger than 34 months with ASD diagnosed by a child and adolescent psychiatrist; (2) as a result of a language evaluation, toddlers with speechlessness or delay (less than the 10th percentile compared with their peers); and (3) toddlers with Korean-Childhood Autism Rating Scale (K-CARS-2) scores of 30 or higher. Those who satisfied at least two of the above three criteria were included in this study. Fifteen pairs in the experimental group (12 boys and three girls; mean age, 29.7 months) and nine pairs in the control group (six boys and three girls; mean age, 30.1 months) participated in the study (Supplementary Table 1). The Levene test for equality of variance showed that the assumption of homogeneity of variance had not been violated for measures of age ($t=-0.289$, $P>0.05$) and
K-CARS-2 scores (t=–0.716, P>0.05). There were two babies born prematurely (34±6, 36±1 weeks) in the experimental group and three (31, 34, 35 weeks) in the control group. There were no subjects with neurological diseases, including epilepsy, in either groups. The treatment intervention was defined as “a treatment to alleviate ASD, such as play therapy, language therapy, and sensory integration therapy, at least once a week for at least 3 months.” In the experimental group, no participants received other interventions. In the control group, only one participant received speech therapy and sensory integration therapy. There were no statistically significant differences between the two groups in terms of prematurity, history of neurological disease, and history of interventions for ASD. The researchers explained to the parents the purpose of the study and gave them brief guidance on the program. Parents who agreed with the procedures of the study signed an informed consent form and received an explanation that their personal information would remain confidential. The control group received no parent education program. The study period was from September 2020 to August 2021. This research was approved by the Medical Sciences Ethics Committee of Ilsan Medical Center (IRB file No. 2020-04-018).

2. Methods

1) A hospital-provided hybrid parental support program

The hospital-provided hybrid parental support program was designed to reinforce parents’ capabilities and promote the development of toddlers with or at risk of ASD by delivering information to their parents and supporting the implementation of interventions. To construct the content and methods of this program, published NDBI manuals for young children with ASD, such as the Social Communication Emotional Regulation Transactional Support, were reviewed, focusing on the needs for parental support, the implementation method that parents want, and the teaching strategies of the existing parent support programs [10,11,20]. The specific implementation stages and content of the parental support program were organized as shown in Fig. 1.

The researchers of this study led the first to third and eighth group sessions in hospitals, and the risk of mass infection was minimized by separating the seats by 2 m and requiring all participants to wear a mask. The fourth to seventh sessions were conducted online using Zoom, an online-based platform, by a member of the research team with a PhD in the field of special education and autism. In the first and second sessions, rapport with participants was formed, and education on the characteristics of toddlers with ASD and early developmental features was covered. Parents watched extensive video footage from a web-based instructional program developed by the Florida State University Autism Institute. Observations, discussions, and questions and answers were conducted in the order of homework guidance. During the third session, the researchers helped parents set intervention goals based on the child’s behavioral observation data collected by parents in their daily lives. From the fourth to seventh sessions, the member of the research term with a PhD in special education conducted individual online sessions for about 90 minutes per week. Each week, the recent status was shared with parents who observed their children’s behavior, and a teaching plan that could be implemented in daily life was established following the progress of each session. In the fourth session, an interaction strategy that included following the child’s interest and imitating the child’s actions and verbalizations was covered. In the fifth session, behavioral teaching strategies, such as using natural reinforcement, time-delay, and the mand-model, were introduced. In the sixth session, information on children’s different sensory preferences, the types of play that reflects sensory profiles, and modeling were covered. In the seventh session, the use of visual support strategies and picture exchange communication systems was introduced, and all teaching strategies were reflected in the intervention plan. The researchers guided them to carry out interventions at home from the end of the session until the day the next session began. In the last session, group education was conducted at the hospital, reviewing the teaching strategies and providing

![Fig. 1. An overview of a hospital-provided hybrid parental support program. The program comprised four components: understanding early development, learning about autism spectrum disorder (ASD) features, carrying out evidence-based practices, and 1:1 coaching and support from professionals.](https://doi.org/10.26815/acn.2022.00381)
guidance for future directions of interventions. The roles of the researchers and parents in each session are shown in Table 1.

2) Measures
In this study, the Early Social Communication Scales (ESCS) [21], K-CARS-2 [22], Korean Vineland Adaptive Behavior Scales-II (K-Vineland-II) [23], and the Korean version of Child Behavior Checklist for Ages 1.5–5 (K-CBCL 1.5–5) [24] were used to examine the key autism-related characteristics of toddlers with or at risk of ASD. The ESCS is a semi-structured observation measurement tool developed by Mundy and Gomes [21] to evaluate the nonverbal communication capabilities of infants and toddlers aged

<table>
<thead>
<tr>
<th>Week</th>
<th>Content</th>
<th>Parent’s weekly assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2</td>
<td>Guide program and plan description</td>
<td>Review session 1 and 2</td>
</tr>
<tr>
<td></td>
<td>Describe the development and behavioral characteristics of toddlers with ASD</td>
<td>Fill in basic information</td>
</tr>
<tr>
<td></td>
<td>Share and discuss cases after watching related content</td>
<td>Observe the child’s behavior</td>
</tr>
<tr>
<td></td>
<td>Review session on SNS—guidance on tasks, and information about the next session</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Describe the development and behavioral characteristics of toddlers with ASD</td>
<td>Review session 3</td>
</tr>
<tr>
<td></td>
<td>Share and discuss cases after watching related content</td>
<td>Find the child’s favorite toy, play, activities</td>
</tr>
<tr>
<td></td>
<td>Introduce and teach how to operate an online session</td>
<td>Structuring a system within the family</td>
</tr>
<tr>
<td></td>
<td>Review session on SNS—guidance on tasks, and information about the next session</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Checkup on assignments and status update</td>
<td>Review session 4</td>
</tr>
<tr>
<td></td>
<td>Review sessions 1–3</td>
<td>Plan and practice</td>
</tr>
<tr>
<td></td>
<td>Guide on how to initiate and create interactions including following child’s lead and imitating his/her actions and verbalizations</td>
<td>Share treatment integrity record with the researcher</td>
</tr>
<tr>
<td></td>
<td>Establish an action plan for parents to reflect on the content of each session</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Check the level of difficulty of the plan and coordinate with the parents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q&amp;A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Review session on SNS—guidance on tasks, and information about the next session</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Checkup on assignments and status update</td>
<td>Review session 5</td>
</tr>
<tr>
<td></td>
<td>Review session 4</td>
<td>Plan and practice</td>
</tr>
<tr>
<td></td>
<td>Establish an action plan for parents to reflect on the content of each session</td>
<td>Share treatment integrity record with the researcher</td>
</tr>
<tr>
<td></td>
<td>Guide play-based activities and behavioral strategies such as natural reinforcement, time-delay, mand-model for support</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Check the level of difficulty of the plan and coordinate with the parents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q&amp;A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Review session on SNS—guidance on tasks, and information about the next session</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Checkup on assignments and status update</td>
<td>Review session 6</td>
</tr>
<tr>
<td></td>
<td>Review session 5</td>
<td>Plan and practice</td>
</tr>
<tr>
<td></td>
<td>Establish an action plan for parents to reflect on the content of each session</td>
<td>Share treatment integrity record with the researcher</td>
</tr>
<tr>
<td></td>
<td>Introduce the sensory characteristics and the types of play</td>
<td>Ascertain the visual support to learn about in session 7</td>
</tr>
<tr>
<td></td>
<td>Check the level of difficulty of the plan and coordinate with the parents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q&amp;A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Review session on SNS—guidance on tasks, and information about the next session</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Checkup on assignments and status update</td>
<td>Review session 7</td>
</tr>
<tr>
<td></td>
<td>Review session 6</td>
<td>Plan and practice</td>
</tr>
<tr>
<td></td>
<td>Establish an action plan for parents to reflect on the content of each session</td>
<td>Share treatment integrity record with the researcher</td>
</tr>
<tr>
<td></td>
<td>Show strategies using visual support and levels of prompts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Check the level of difficulty of the plan and coordinate with the parents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q&amp;A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Review session on SNS—guidance on tasks, and information about the next session</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>General overview of all the sessions</td>
<td>Review session 7</td>
</tr>
<tr>
<td></td>
<td>Modifying the intervention plan and communicating information</td>
<td>Plan and practice</td>
</tr>
<tr>
<td></td>
<td>Complete the program with an appreciation note through SNS</td>
<td>Share treatment integrity record with the researcher</td>
</tr>
</tbody>
</table>

ASD, autism spectrum disorder; SNS, social networking service.
8 to 30 months. The ESCS has been used to evaluate the social communication skills of infants and toddlers with ASD in previous studies. The interrater reliability was reported in previous studies [25] to be 91, and the variables measured in this study were the total frequency of responding to joint attention (RJA) and initiating joint attention (IJA). To evaluate changes in parental behavior, the measurements and results were analyzed using the Toddler Care Questionnaire (TCQ) [26] and the Korean Parenting Stress Index Short Form (K-PSI-SF) [27]. This was conducted twice, once before and once after the parental support program (Supplementary Table 2) [22,23,28-31].

3) Experimental design and procedures
A pretest-posttest control group design was used to ascertain whether behavioral changes between the two groups differed significantly. The control group received no education program or support over the same period of time.

4) Observer training and interobserver reliability
Before evaluating changes in the joint attention behavior of toddlers in the experimental group, the reliability between observers was secured by conducting observer training. After familiarization with the items of the ESCS and the operational definition for each question, two observers observed video clips of toddlers in the risk group who did not participate in this study, and further evaluated their behavior. The reliability between observers was calculated as an equivalent correlation coefficient (r). It has been recommended to conduct observer training until an r of 0.85 or higher is reached [32], while referring to the criteria of previous studies [25]. The training was terminated when r was 0.91. The evaluation was conducted by two observers, one from the research team and one who was not involved in other aspects of the study and was blind to both pretest and posttest conditions. The observers coded the video clips according to ESCS manual. The correlation coefficient between observers for the evaluation results was 0.90 for the pretest and 0.91 for the posttest.

5) Social validity for the study
To examine the social validity of the study, parents were asked to rate and score 15 questions on the appropriateness of the content, teaching strategies, education programs, appropriateness of procedures and methods, and competency reinforcing and generalization through the intervention, on a 5-point scale.

6) Intervention fidelity of the study
Intervention fidelity was evaluated by the researcher, Minkyung Suh by checking the record sheet to ascertain whether the researcher operated according to the plan for group education and one-on-one online sessions. The evaluation sheet comprised a total of 23 questions. Implemented or non-implemented items were recorded as “O” and “X” respectively. If not applicable, the items were recorded as “NA” (Table 2). Parent participants were evaluated by checking the treatment integrity record sheet to ascertain whether the intervention was carried out according to the plan from the fourth session conducted online. The fidelity of the parental intervention was calculated by recording 15 questions as “O” for items implemented by parents, and “X” for non-implemented questions (Table 3). The researcher, MinKyung Suh self checked the intervention fidelity form the intervention inspection data during the next visit.

3. Statistical analysis
Data were analyzed using the Korean version of SPSS version 25.0 (IBM Corp., Armonk, NY, USA). The Mann-Whitney U test was used to compare differences between two groups, with significance accepted at a P value <0.05. The Wilcoxon rank test was used to compare the pretest and posttest differences between the experimental group and the control group.

Results

1. Changes in the behaviors of toddlers and parents in the experimental group
In the experimental group, the IJA scores on the ESCS increased from 21.34 to 32.08, the RJA score increased from 35.70±29.58 to 59.04±21.34, the difference was statistically significant (P<0.01). The adaptive behavior composite score of the K-CARS-2 decreased from 28.67±4.03 to 22.70±6.33; this difference was also statistically significant (P<0.01). The K-Vineland-II decreased from 71.47±10.10 to

Table 2. Results of the researcher’s intervention fidelity test

<table>
<thead>
<tr>
<th>Session no.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>Average (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage (%)</td>
<td>92.2</td>
<td>93.3</td>
<td>95</td>
<td>98.2</td>
<td>97.4</td>
<td>95.1</td>
<td>98.1</td>
<td>97.2</td>
</tr>
</tbody>
</table>

Table 3. Results of the participating parents’ intervention fidelity test for online sessions

<table>
<thead>
<tr>
<th>Session no.</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage (%)</td>
<td>81.3</td>
<td>78.2</td>
<td>83.5</td>
<td>82.2</td>
</tr>
</tbody>
</table>
69.47±11.65; the difference was not statistically significant. The total behavior composite score of the K-CBCL 1.5–5 decreased from 58.33±14.67 to 56.80±16.46; the difference was not statistically significant.

The parenting efficacy increased from 121.40±36.14 to 145.20±18.56; the difference was statistically significant (P<0.05). The parenting stress level of the experimental group increased from 95.07±19.54 to 98.33±21.50; this difference was likewise not statistically significant (Table 4).

2. Changes in the behavior of toddlers and parents in the control group
In the control group, from the pretest to the posttest, the K-CARS-2 scores decreased from 28.1±3.30 to 27.44±2.92; the difference was not statistically significant. The total behavior composite score of the K-CBCL 1.5–5 increased from 53.00±12.12 to 54.00±16.16; this difference was likewise not statistically significant.

The parenting efficacy increased from 133.56±11.57 to 136.11±17.24, and this difference was not statistically significant. The parenting stress level decreased from 95.44±17.19 to 89.22±17.24; this difference was also not statistically significant (Table 5).

3. Changes in the behavior of toddlers and parents between the experimental and control group
The difference in K-CARS-2 scores between the experimental and the control groups was statistically significant (Z=–2.63 and P<0.01). However, the difference in total behavior problem scores of the K-CBCL 1.5–5 between the two groups was not statistically significant.

The difference in parenting efficacy between the experimental and the control groups was statistically significant (Z=–2.12 and P<0.05). However, the difference in parenting stress between the two groups was not statistically significant (Table 6).

4. Social validity
The overall average score on the social validity test, which requested the study participants to evaluate the overall program, was 4.56. Accordingly, it is safe to conclude that the parent participants were generally satisfied with the support program.

Discussion
The toddler participants in the experimental group showed significant improvements in their joint attention scores of the ESCS and K-CARS-2 scores from the pretest to the posttest. Additionally, parent participants showed a between-group difference in parent-

<table>
<thead>
<tr>
<th>Evaluation area</th>
<th>Experimental group (n=15)</th>
<th>Control group (n=9)</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toddlers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K-CARS-2</td>
<td>28.11±3.30</td>
<td>27.44±2.92</td>
<td>−0.54</td>
</tr>
<tr>
<td>Total behavior problem scores of K-CBCL 1.5–5</td>
<td>53.00±12.12</td>
<td>54.00±16.16</td>
<td>−0.25</td>
</tr>
<tr>
<td>Parents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenting efficacy</td>
<td>133.56±11.57</td>
<td>136.11±12.21</td>
<td>−0.77</td>
</tr>
<tr>
<td>Parenting stress</td>
<td>95.44±17.19</td>
<td>89.22±17.24</td>
<td>−1.25</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation.
Table 6. Changes in the behaviors of toddlers and parents between the experimental and control groups

<table>
<thead>
<tr>
<th>Evaluation area</th>
<th>Experimental group (n=15)</th>
<th>Control group (n=9)</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretest</td>
<td>Posttest</td>
<td>Differences</td>
</tr>
<tr>
<td>K-CARS-2</td>
<td>28.67±4.03</td>
<td>22.72±6.34</td>
<td>-5.97±4.66</td>
</tr>
<tr>
<td>Total behavior problem score of K-CBCL 1.5–5</td>
<td>58.33±14.67</td>
<td>56.80±16.46</td>
<td>-1.53±8.62</td>
</tr>
<tr>
<td>Parenting efficacy</td>
<td>130.07±16.46</td>
<td>145.20±18.57</td>
<td>15.13±17.03</td>
</tr>
<tr>
<td>Parenting stress</td>
<td>95.07±19.54</td>
<td>98.33±21.50</td>
<td>3.27±15.13</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation.

First, this hospital-provided hybrid parental support program increased the joint attention skills of toddlers in the experimental group, and the difference between the pretest and posttest was statistically significant (P<0.01). This promising finding is consistent with a previous study by Kasari et al. [5], who reported the improvement of joint attention skills in toddlers via PIs. Parents who participated in the study developed an overall understanding of ASD at 1 to 3 weeks by observing their children and learning specific strategies through an online session that lasted for 4 weeks. The fact that parents followed their children's interests induced joint attention using preferred toys and provided repeated opportunities in their daily lives, which is believed to have influenced the increase in joint attention skills.

Second, the adaptive behavior, emotions, and behaviors of toddlers in the experimental group decreased. However, the difference between the pretest and the posttest was statistically insignificant. This result differs from the effect of online training on parents of toddlers with ASD for 12 weeks reported by Vismara et al. [33]. It appears that the 8-week period in this study was insufficient to achieve statistically significant results [33].

Third, the parenting efficacy of parents who participated in this study increased, and the between-group difference was statistically significant. This supports related studies [11,34], according to which a program conducted on toddlers with ASD and their parents affected parental parenting efficacy. In many cases, parents of ASD children said that poor information after diagnosis and the widely varying opinions of many experts delayed educational decisions and negatively affected parenting efficacy [35].

Fourth, the parenting stress level decreased over time for parents in the control group, whereas it increased in the experimental group. This finding is consistent with the results of a previous study that compared two parent education programs [5]. Parents came to better understand their children's behavior during the online sessions, but the fact that they had to do homework and conduct interventions might have been a burden. It is believed that the parents' feelings of worrying about their children's behavior while conducting the intervention affected parenting stress. There are mixed research results on parenting stress depending on the child's age, parents' experiences, parents' disability acceptance level, and the dose of the intervention [5,14]. Among these, the frequency and length (dose) of the intervention may be important factors in improving outcomes for parent stress [36]. It is therefore assumed that an extended parent education program would significantly contribute to relieving parenting stress.

The clinical implications of these findings are as follows. First, parents of young children with ASD are able to implement interventions daily. Second, a hybrid parent education format is an alternative to efficiently operate the program under circumstances where it is challenging to visit hospitals or have professionals visit homes owing to COVID-19. Third, professional support seems to have reinforced the parents' ability to implement interventions. From the first session, parents observed their child's behaviors, types of play, preferred play objects, and were able to gradually increase the amount of cooperative play time by merging various teaching strategies.

The limitations of this study are as follows. First, toddlers older than 34 months at the start of the study could not participate in this study. Due to the small number of participants, this study could not be conducted as a randomized controlled trial, which remains a limitation of the study. Second, a limited number of parents were recruited, which is a drawback. In subsequent studies, it will be necessary to examine the effects on joint attention, adaptive behavior, emotion, and behaviors comprehensively, using a larger group of participants from various regions. Third, the parents had to visit hospitals to participate in the children's tests and group education. Conducting the sessions at a preferred time could result in high participation.
Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.26815/acn.2022.00381.

Conflicts of interest

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

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Real-Life Efficacy and Tolerability of Lacosamide in Pediatric Patients Aged 4 Years or Older with Drug-Resistant Epilepsy

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\textbf{Purpose:} The aim of this study was to evaluate the efficacy and safety of adjunctive lacosamide therapy in pediatric patients aged ≥4 years with drug-resistant epilepsy (DRE).

\textbf{Methods:} Medical records of children aged 4 to 19 years treated with lacosamide as adjunctive therapy for DRE were retrospectively reviewed. The patients were divided into two groups according to their age at the start of lacosamide treatment: group A (aged 4–15 years) and group B (aged 16–19 years). Changes in seizure frequency from baseline, adverse events, and the retention rate were evaluated at each follow-up visit.

\textbf{Results:} Sixty-two patients (33 males and 29 females) with a mean age of 11.4 years (range, 4 to 19) were included. The mean duration of follow-up was 20.1±12.9 months. The mean maintenance dose of lacosamide was 6.7±4.8 mg/kg/day. Forty-two patients (67.7%) were responders (≥50% reduction in seizures) with 19.4% (12/62) achieving freedom from seizures. The response rate did not differ significantly between groups A and B (67.6% vs. 68.0%, \(P=0.795\)) and was not affected by the concomitant use of sodium channel blockers. Significant independent factors associated with a good response to lacosamide treatment were a shorter duration of epilepsy (\(P=0.035\)) and fewer concomitant anti-seizure medications (\(P=0.002\)). Mild transient adverse events were observed in 20 patients (32.3%).

\textbf{Conclusion:} Lacosamide adjunctive therapy was efficacious and tolerated in children aged ≥4 years with DRE. Early use of lacosamide may be helpful for a good response to drug-resistant seizures.

\textbf{Keywords:} Lacosamide; Anticonvulsants; Child; Pediatrics; Epilepsy

\textbf{Introduction}

Approximately 25% to 30% of children with epilepsy have drug-resistant seizures or experience significant adverse events (AEs), despite the introduction of multiple new anti-seizure medications (ASMs) over the past 20 years [1]. Such drug-resistant epilepsy...
(DRE) leads to prominent risks of neuronal damage and cognitive decline in these patients; therefore, novel, effective, and well tolerated ASM therapies are urgently required to improve treatment outcomes. Lacosamide (LCM) is an ASM that exerts anticonvulsant activity by selectively enhancing slow inactivation of voltage-gated sodium channels [2]. LCM has high oral absorption with linear pharmacokinetics, low protein binding, good renal clearance, and low potential for drug-drug interactions [3]. LCM was approved for the treatment of focal seizures in patients aged ≥4 years in the United States and European Union in 2017.

In adults, several randomized controlled trials have demonstrated the efficacy and tolerability of LCM as adjunctive therapy and monotherapy for uncontrolled focal seizures [4,5], with further support from experience in clinical practice [6]. However, the effectiveness of adjunctive LCM in children and adolescents has been investigated in a few observational [7-14] or prospective studies [15,16] and only one double-blind randomized controlled trial (Supplementary Table 1) [17]. Among these studies, only three were conducted in Asia [9,10,13], and only two other studies included patients with general seizures and focal seizures [11,16].

Herein, we present our experience with adjunctive LCM therapy in pediatric patients aged ≥4 years with DRE at a single tertiary center. To the best of our knowledge, this is the largest long-term study of a pediatric population in East Asia.

Materials and Methods

1. Patients
In this retrospective cohort study, we retrospectively reviewed the electronic medical records of patients treated with oral LCM as an adjunctive treatment for focal epilepsy at Pusan National University Children’s Hospital between May 2018 and April 2022. Patients were selected based on the following criteria: (1) ≥4 years to <20 years of age; (2) being affected by drug-resistant seizures; (3) exhibiting at least one seizure per month during the 6 months before LCM was administered; and (4) concomitant ASMs being unchanged for the duration of the study. Patients with progressive neurological disorders and those with insufficient medical records were excluded from the study.

2. Data collection and evaluation for treatment outcomes of LCM
The following data were collected: sex; seizure types; presence of intellectual disability, etiology of epilepsy; history of ketogenic diet, vagus nerve stimulation (VNS), or epilepsy surgery; age at seizure onset; age at initiation of ASM use; age at initiation of LCM use; duration of epilepsy; duration of LCM treatment; number of ASMs previously administered; monthly seizure frequency; initial daily dose of LCM; final maintenance dose of LCM; retention at the end of the study; and AEs. The optimal maintenance dose of LCM was determined for each patient, depending on the clinical response and tolerability. Seizure types were classified as generalized, focal, combined focal, and generalized. Epilepsy etiologies were classified into genetic, metabolic, infectious, structural, and unknown based on the new classification of seizures and epilepsy by the International League Against Epilepsy (2022).

The response to LCM treatment was assessed based on the mean monthly seizure frequency during the follow-up period over the last 6 months. It was classified as seizure-free (100% reduction), 50%–99% reduction, 1%–49% reduction, and no change in monthly seizure frequency. A good response was defined as ≥50% reduction (seizure-free or 50% to 99% reduction). Patients with a good response were considered responders, and all patients with a <50% reduction in seizure frequency were designated as non-responders. The patients were divided into two groups according to age at the start of LCM: group A (4–15 years of age) and group B (16–19 years of age). We obtained information on changes in seizure frequency compared with baseline, AEs, and discontinuation and retention rates at each follow-up visit.

3. Statistics
All analyses were performed using R software version 3.2.1 meta package (R Foundation for Statistical Computing, Beijing, China), and all statistical tests were two-sided. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the effect of ASMs on all dichotomous outcomes. Multivariate logistic regression was used to identify factors independently associated with a good response to LCM treatment. ORs with 95% CIs were used to test for differences within groups. In all analyses, P values of <0.05 indicated statistical significance.

4. Standard protocol approvals and patient consent
Ethical approval for this study was provided by the Institutional Review Board of Pusan National University Yangsan Hospital (number: 05-2023-038). Informed consent was obtained from all the participants.

Results

1. Demographic and clinical profile of the patients
This study recruited 62 children and adolescents, comprising 33
males and 29 females with ages ranging between 4 and 19 years (mean, 11.4±8.2) at the initiation of LCM treatment (Table 1). The mean age at the first seizure was 7.1 years (range, 2.8 to 13.8), and the mean period between seizure onset and ASM initiation was 1.6 years (range, 0.3 to 5.9). The mean seizure frequency was 19.8 per month (range, 2 to 66). The starting dosage of LCM was 1.7±1.2 mg/kg/day, and the final maintenance dosage was 6.7±4.8 mg/kg/day. The retention rate at the end of the study was 80.6%.

Table 1 presents the demographic characteristics and clinical features of groups A and B when they were started on LCM. There were no significant differences between groups A and B in the sex ratio (male ratio, 54.1% vs. 52.0%, P=0.503); seizure type; etiologies; history of ketogenic diet (8.1% vs. 8.0%, P=0.483); VNS (13.5% vs. 8.0%, P=0.151); epilepsy surgery (2.7% vs. 0.0%, P=0.931); period between seizure onset and ASM initiation (1.5±1.8 years vs. 1.9±2.2 years, P=0.087); period between ASM initiation and starting LCM (2.1±1.8 years vs. 3.1±2.7 years, P=0.074), duration of LCM treatment (19.9±11.8 months vs. 20.8±12.2 months, P=0.643), number of ASMs previously administered (2.9±4.3 vs. 4.3±2.9, P=0.120), initial daily dose of LCM (1.7±1.4 mg/kg vs. 1.8±1.5 mg/kg, P=0.721); daily maintenance dose of LCM (6.2±4.7 mg/kg vs. 7.5±4.9 mg/kg, P=0.132); or the retention rate (78.4% vs. 84.0%, P=0.583). In contrast, the patients in group A had a higher proportion of intellectual disability (67.6% vs. 40.0%, P=0.032) and a higher baseline monthly seizure frequency (26.4±38.3 vs. 12.8±18.3, P=0.011) than those in group B. The mean ages at seizure onset (4.9±3.2 years vs. 10.3±8.7 years, P=0.001) and LCM initiation (8.0±6.9 years vs. 16.4±12.7 years, P<0.001) were significantly different between groups A and B.

Table 1. Comparison of demographic profiles and clinical features between groups A (aged 4–15 years) and B (aged 16–19 years), according to age at lacosamide initiation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=62)</th>
<th>Group A (n=37)</th>
<th>Group B (n=25)</th>
<th>Pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>33 (53.2)</td>
<td>20 (54.1)</td>
<td>13 (52.0)</td>
<td>0.503</td>
</tr>
<tr>
<td>Type of seizures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>50 (80.6)</td>
<td>31 (83.8)</td>
<td>19 (76.0)</td>
<td>0.447</td>
</tr>
<tr>
<td>Generalized</td>
<td>7 (11.3)</td>
<td>4 (10.8)</td>
<td>3 (12.0)</td>
<td>0.885</td>
</tr>
<tr>
<td>Combined</td>
<td>5 (8.1)</td>
<td>2 (5.4)</td>
<td>3 (12.0)</td>
<td>0.350</td>
</tr>
<tr>
<td>Intellectual disability</td>
<td>35 (56.5)</td>
<td>25 (67.6)</td>
<td>10 (40.0)</td>
<td>0.032</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic/metabolic</td>
<td>3 (4.8)</td>
<td>1 (2.7)</td>
<td>2 (8.0)</td>
<td>0.340</td>
</tr>
<tr>
<td>Infection</td>
<td>5 (8.1)</td>
<td>4 (10.8)</td>
<td>1 (4.0)</td>
<td>0.334</td>
</tr>
<tr>
<td>Structural</td>
<td>19 (30.6)</td>
<td>13 (35.1)</td>
<td>6 (24.0)</td>
<td>0.351</td>
</tr>
<tr>
<td>Unknown</td>
<td>35 (56.5)</td>
<td>19 (51.4)</td>
<td>16 (64.0)</td>
<td>0.324</td>
</tr>
<tr>
<td>Ketogenic diet</td>
<td>5 (8.1)</td>
<td>3 (8.1)</td>
<td>2 (8.0)</td>
<td>0.483</td>
</tr>
<tr>
<td>Vagus nerve stimulation</td>
<td>7 (11.3)</td>
<td>5 (13.5)</td>
<td>2 (8.0)</td>
<td>0.151</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>1 (1.6)</td>
<td>1 (2.7)</td>
<td>0</td>
<td>0.931</td>
</tr>
<tr>
<td>Age at seizure onset (yr)</td>
<td>7.1±6.8</td>
<td>4.9±3.2</td>
<td>10.3±8.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Period between seizure onset and ASM initiation (yr)</td>
<td>1.6±1.9</td>
<td>1.5±1.8</td>
<td>1.9±2.2</td>
<td>0.087</td>
</tr>
<tr>
<td>Period between ASM initiation and LCM initiation (yr)</td>
<td>2.6±2.2</td>
<td>2.1±1.8</td>
<td>3.1±2.7</td>
<td>0.074</td>
</tr>
<tr>
<td>Age at LCM initiation (yr)</td>
<td>11.4±8.2</td>
<td>8.0±6.9</td>
<td>16.4±12.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of LCM treatment (mo)</td>
<td>20.1±12.9</td>
<td>19.9±11.8</td>
<td>20.8±12.2</td>
<td>0.643</td>
</tr>
<tr>
<td>Number of ASMs administered</td>
<td>3.5±2.3</td>
<td>2.9±1.4</td>
<td>4.3±2.9</td>
<td>0.120</td>
</tr>
<tr>
<td>SCBs</td>
<td>39 (62.9)</td>
<td>22 (59.5)</td>
<td>17 (68.0)</td>
<td>0.381</td>
</tr>
<tr>
<td>Seizure frequency (/mo)</td>
<td>19.8±31.9</td>
<td>26.4±38.3</td>
<td>12.8±18.3</td>
<td>0.011</td>
</tr>
<tr>
<td>Initial dose of LCM (mg/kg/day)</td>
<td>1.7±1.2</td>
<td>1.7±1.4</td>
<td>1.8±1.5</td>
<td>0.721</td>
</tr>
<tr>
<td>Maintenance dose of LCM (mg/kg/day)</td>
<td>6.7±4.8</td>
<td>6.2±4.7</td>
<td>7.5±4.9</td>
<td>0.132</td>
</tr>
<tr>
<td>Retention rate</td>
<td></td>
<td></td>
<td></td>
<td>0.377</td>
</tr>
<tr>
<td>Maintenance</td>
<td>50 (80.6)</td>
<td>29 (78.4)</td>
<td>21 (84.0)</td>
<td>0.583</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>11 (17.7)</td>
<td>7 (19.9)</td>
<td>4 (16.0)</td>
<td>0.768</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>1 (1.6)</td>
<td>1 (2.7)</td>
<td>0</td>
<td>0.407</td>
</tr>
<tr>
<td>Causes of discontinuation</td>
<td>11 (17.7)</td>
<td>7 (19.9)</td>
<td>4 (16.0)</td>
<td>0.678</td>
</tr>
<tr>
<td>Adverse events</td>
<td>4 (6.5)</td>
<td>2 (5.4)</td>
<td>2 (8.0)</td>
<td>0.362</td>
</tr>
<tr>
<td>Ineffective</td>
<td>7 (11.3)</td>
<td>4 (10.8)</td>
<td>3 (12.0)</td>
<td>0.691</td>
</tr>
</tbody>
</table>

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

ASM, anti-seizure medication; LCM, lacosamide; SCB, sodium channel blocker (carbamazepine, lamotrigine, oxcarbazepine, or phenytoin).

*P<0.05 (group A vs. group B).
P<0.001) were significantly lower in group A patients than those in group B (Table 1).

2. Efficacy

Of the 62 patients, the proportions of patients who were seizure-free (100% reduction), experienced a 50% to 99% reduction in seizure frequency, and were classified as responders (≥50% reduction) were 19.4% (12/62), 48.4% (30/62), and 67.7% (42/62), respectively (Fig. 1). The response rate did not differ significantly between groups A and B (67.6% vs. 68.0%, P=0.795). Thirty-nine patients (62.9%) used sodium channel blockers (SCBs; carbamazepine, lamotrigine, oxcarbazepine, or phenytoin) as part of combination therapy. There was no significant difference in the response rate between patients who did and did not receive concomitant SCBs (64.8% vs. 70.3%, P=0.597) (Fig. 2).

The demographic and outcome data of responders and non-responders were investigated and analyzed (Table 2). The responders were significantly older at seizure onset (7.9±5.7 years vs. 5.6±4.5 years, P=0.038) and ASM initiation (9.4±5.3 years vs. 7.4±5.1 years, P=0.041) than the non-responders. The responders had a significantly shorter duration of epilepsy (1.8±1.2 years vs. 4.4±2.9 years, P=0.015) and a significantly longer duration of LCM treatment (17.8±9.3 months vs. 10.7±6.9 months, P=0.039) than the non-responders. The proportion of patients with intellectual disability (47.6% vs. 75.0%, P=0.042) and the number of ASMs administered (2.8±1.6 vs. 4.9±2.3, P=0.006) were conspicuously lower in the responders than in the non-responders. The responders showed a significantly lower discontinuation rate (7.1% vs. 40.0%, P=0.002) than the non-responders. Ten patients with Lennox-Gastaut syndrome and four with sleep-related hypermotor epilepsy were classified as having epilepsy syndrome (Table 2). Of the 10 patients with Lennox-Gastaut syndrome, eight were responders, and two of them were seizure-free. All four patients with sleep-related hypermotor epilepsy were responders, and two of them remained seizure-free.

In a logistic regression model of the independent significant factors affecting the seizure outcomes of adjunctive LCM therapy (Table 3), a good response (≥50% reduction) was significantly negatively correlated with the duration of epilepsy (P=0.035) and...
The number of ASMs previously administered (P=0.002). The number of ASMs (P=0.013) and baseline seizure frequency (P=0.046) were significant factors that negatively affected the likelihood of freedom from seizures.

### 3. Safety and tolerability

At least one AE was reported in 20 patients (32.3%) (Table 4), and some AEs appeared simultaneously. The mean dosage at which AEs occurred was 11.5±10.2 mg/kg/day. Somnolence was the most common AE (12/62 [19.4%]), followed by dizziness (9.7%), nausea (6.5%), headache (4.8%), and anxiety/irritability (1.6%). There was no significant difference between groups A and B in the rate of AEs, dosage at AE appearance, or type of AE (Table 4). No severe or life-threatening AEs were reported in this study. All AEs were tolerable or resolved in time through dose reduction or LCM discontinuation. There were no significant laboratory anomalies in liver function, renal function, or hematological examinations.

LCM was discontinued at similar rates in groups A and B (18.9% vs. 16.0%, P=0.678) (Table 1). The rate of discontinuation due to AEs was not significantly different between the two groups (5.4% vs. 8.0%, P=0.362). There was no significant difference in the discontinuation rate according to whether patients did or did not receive SCBs (8/39 [20.5%] vs. 3/23 [13.0%], P=0.457; data not shown).

The efficacy, tolerability, and significant independent factors af-
flecting a good response to LCM treatment in children and adolescents aged ≥4 years with DRE are summarized in Fig. 3.

### Discussion

In this retrospective study, adjunctive LCM therapy was effective in reducing seizure frequency and was generally well tolerated in 62 children and adolescents (aged ≥4 to ≤19 years) with DRE. The rate of response (≥50% reduction in seizures) was 67.7% (42/62), with 19.4% (12/62) achieving freedom from seizures; this proportion did not differ significantly according to age (4–15 years vs. 16–19 years; 67.6% vs. 68.0%, P = 0.795). The response rate of LCM was similar in both groups, regardless of whether a concomitant SCB was used (64.8% vs. 70.3%, P = 0.597). Significant factors affecting a good response to seizure reduction were a shorter duration of epilepsy (P = 0.035) and fewer ASMs previously administered (P = 0.002). At least one AE was reported in 32.3% (20/62) of the patients. All the AEs were mild and transient, and no severe or life-threatening AEs were reported. To the best of our knowledge, this study is based on real-life clinical practice and reflects the efficacy and AEs of LCM in the largest population of pediatric patients with drug-resistant focal and/or generalized epilepsy studied to date, with the longest follow-up duration of LCM treatment (20.1±12.9 months), at a single tertiary center in East Asia.

LCM has been approved by the licensing authorities in the European Union and in the United States as monotherapy for focal seizures in patients ≥1 month of age and as add-on therapy for generalized seizures in patients ≥4 years of age. However, in Korea, LCM has been approved as an add-on therapy for focal seizures in patients aged >16 years. This has resulted in very little research on the outcomes of LCM treatment in pediatric patients. Approval for

### Table 3. Logistic regression model for independent factors affecting seizure outcomes of lacosamide treatment

| Factors                        | Estimate | Standard error | Pr (>|z|) | OR (95% CI)|
|--------------------------------|----------|----------------|----------|------------|
| **Good response**              |          |                |          |            |
| Intellectual disability        | -0.078   | 0.0451         | 0.062    | 0.94 (0.85–1.00) |
| Duration of epilepsy           | -0.508   | 0.2167         | 0.035    | 0.61 (0.36–0.92) |
| Number of ASMs                 | -0.349   | 0.1114         | 0.002    | 0.52 (0.51–0.89) |
| **Freedom from seizures**      |          |                |          |            |
| Number of ASMs                 | -0.779   | 0.1716         | 0.013    | 0.41 (0.41–0.73) |
| Seizure frequency              | -0.026   | 0.0126         | 0.046    | 0.95 (0.78–0.98) |

Pr, probability; OR, odds ratio; CI, confidence interval; ASM, anti-seizure medication.

### Table 4. Adverse events and profiles between groups A (aged 4–15 years) and B (aged 16–19 years) according to age at lacosamide initiation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=62)</th>
<th>Group A (n=37)</th>
<th>Group B (n=25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>20 (32.3)</td>
<td>11 (29.7)</td>
<td>9 (36.0)</td>
<td>0.072</td>
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<tr>
<td>Dose of LCM at AE onset (mg/kg/day)</td>
<td>11.5±10.2</td>
<td>10.8±7.8</td>
<td>12.7±9.5</td>
<td>0.087</td>
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<tr>
<td>Type of AEs</td>
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<tr>
<td>Somnolence</td>
<td>12 (19.4)</td>
<td>7 (18.9)</td>
<td>5 (20.0)</td>
<td>0.072</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (9.7)</td>
<td>4 (10.8)</td>
<td>2 (8.0)</td>
<td>0.323</td>
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<tr>
<td>Nausea</td>
<td>4 (6.5)</td>
<td>2 (5.4)</td>
<td>2 (8.0)</td>
<td>0.083</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (4.8)</td>
<td>2 (5.4)</td>
<td>1 (4.0)</td>
<td>0.676</td>
</tr>
<tr>
<td>Irritability</td>
<td>1 (1.6)</td>
<td>1 (2.7)</td>
<td>0</td>
<td>1.000</td>
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</tbody>
</table>

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

AE, adverse effect/event; LCM, lacosamide.
pediatric use only occurs with a substantial delay after promising results have been achieved in adults [18].

In adult trials, LCM demonstrated a noteworthy advantage in treating DRE, with 30% to 40% of patients achieving a ≥50% reduction in seizure frequency at doses of 400 to 600 mg/day [4,19]. Since 2010, a few studies have described similar benefits of LCM in children and young adults with DRE [7-15]. In these studies, the mean response rate for ≥50% seizure reduction ranged between 20% and 67%, and the seizure-free rate was 11% to 19%. In a prospective study of 21 pediatric patients with refractory epilepsy of various seizure types, LCM was demonstrated to be an effective ASM [16]. Interestingly, two patients with Lennox-Gastaut syndrome showed a >90% seizure reduction. Although our patients showed a similar age and maintenance dose of LCM compared to those in previous pediatric studies, the rate of responders in our study was 67.7%, which was higher than that in previous studies. The patients in our study showed fewer ASMs (3.5±2.3 vs. 3–7.2) and a shorter duration of epilepsy (2.6±2.2 years vs. 3–9 years) than those in previous studies [7-17]. This was consistent with the results of logistic regression analysis for significant factors affecting the seizure outcomes of adjunctive LCM therapy in our study. Therefore, even in children with DRE, LCM may be more effective in reducing seizures in patients who do not have a long duration of epilepsy or have not used a large number of ASMs. Taken together, this indicates that LCM could have a significant clinical impact on patients with a shorter duration of epilepsy in whom a small number of ASMs has failed. From a different perspective, it might be considered that LCM may elicit a better treatment response in patients with less severe DRE, because patients who have taken a large number of ASMs or have shown longer treatment duration could have a higher degree of intractability to the medication. However, it is difficult to infer this conclusively due to the limitations of our retrospective study.

Previous studies on adjunctive LCM therapy have shown better [20,21] or similar [22] tolerability profiles in adult patients not receiving concomitant SCBs than in those receiving SCBs, such as carbamazepine, oxcarbazepine, or phenytoin. It has been suggested that combinations of ASMs with different mechanisms of action might be more efficacious and/or well tolerated than combinations of ASMs with similar mechanisms of action. A retrospective cohort study of children and adolescents with focal, generalized, or mixed epilepsy (n=223) showed that the use of SCBs was an independent predictor of time to LCM treatment failure [23]. Additionally, analyses of pooled data from double-blind placebo-controlled trials in adults showed a potential for better tolerability of adjunctive LCM when taken without SCBs [24]. However, LCM was efficacious regardless of whether SCBs were part of the concomitant ASM regimen in our study (64.8% vs. 70.3%, P=0.597) (Fig. 2). Unlike other SCBs, LCM does not alter the fast inactivation of voltage-gated sodium channels; instead, it selectively enhances the slow inactivation of voltage-gated sodium channels, thereby increasing the proportion of sodium channels unavailable for depolarization [2]. LCM has a predictable pharmacokinetic profile with high oral bioavailability, minimal protein binding (<15% to 19%), low potential for drug-drug interactions, and good renal clearance [3]. Moreover, LCM has not been shown to induce or inhibit cytochrome P450 enzymes in preclinical and clinical studies [25]. Due to the above differences in mechanisms, adjunctive LCM therapy might be more effective in reducing seizures, even if previous SCBs led to a lower response in terms of seizure reduction. Further prospective investigations of combination treatments with SCBs in a larger number of children are needed.

Multiple clinical pharmacology trials have demonstrated that LCM has favorable characteristics compared to other ASMs [3,25]. It is rapidly absorbed after oral administration, with maximum plasma concentration being reached 0.5 to 4 hours after intake. The pharmacokinetics are linear and dose-proportional, with low inter- and intra-individual variability. A population pharmacokinetic analysis of LCM phase 3 trial data suggested that there were 15%–20% and 20%–30% lower LCM plasma concentrations in the presence of enzyme-inducing ASMs [26]. In children, as in adults, the reduction in plasma concentrations is modest. In our study, the LCM plasma level of each patient was not investigated during the study period; therefore, it was not possible to compare efficacy according to plasma drug levels. In clinical practice, ASMs are usually titrated based on individual efficacy and tolerability and not on concentration, and the maintenance dose of LCM was also determined for each patient depending on the clinical response and tolerability.

The AEs most commonly reported during adjunctive LCM therapy in children were similar to those reported during LCM treatment in adults (e.g., somnolence, dizziness, headache, nausea, and diplopia) [27,28]. Most AEs associated with LCM in adults are dose-related and reversible upon discontinuation or dose reduction [29]. The mean dose of LCM in our study was 11.5 mg/kg/day, and the incidence of AEs was 32.3%, which is similar to that reported in previous studies [12,14,16]. LCM was discontinued in four patients (6.5%) because of somnolence, dizziness, or severe irritability. None of our patients experienced severe to life-threatening AEs or aggravated seizure frequency. Among LCM-treated adults on SCB ASM, discontinuation due to AEs was dose-dependent (200 mg, 5.5%; 400 mg, 14.4%; and 600 mg, 31.0%) and most commonly occurred because of dizziness (7.0%
of patients) [24]. In contrast, adjunctive LCM therapy was well tolerated in our pediatric patients, regardless of whether SCBs were part of the treatment regimen (discontinuation rate, 20.5% vs. 13.0%, P=0.457). Individualized titration and dosing could enable optimization of the tolerability of LCM add-on therapy in children administered various ASM combinations.

This study has some limitations. First, this was a retrospective study involving a rather small number of patients, although this study included the largest number of pediatric patients in East Asia analyzed to date. Second, the effect of dosage and serum concentration of other ASMs on the efficacy of LCM was not investigated. Third, we did not evaluate the effect of LCM on behavioral or neuropsychological outcomes in pediatric patients. Further prospective large-scale studies in young children or infants with DRE are needed to clarify the benefits of LCM in these groups.

In conclusion, our retrospective study demonstrated that adjunctive LCM therapy was efficacious and well tolerated in children aged ≥4 years with drug-resistant focal and/or generalized epilepsy. The response rate of LCM was similar in both groups, regardless of whether a concomitant SCB was used. Significant factors associated with a good response to adjunctive LCM therapy were a shorter duration of epilepsy and fewer ASMs applied. Therefore, early use of LCM may be helpful for a good response in children with DRE.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.26815/acn.2023.00073.

Conflicts of interest

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

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References


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Early Successful Treatment in a Child with Febrile Infection-Related Epilepsy Syndrome

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1Pediatric Neurology Department, São João University Hospital Center, Porto, Portugal
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Febrile infection-related epilepsy syndrome (FIRES) is an extremely rare and dramatic type of epileptic encephalopathy, with an estimated incidence of 1 in 1 million children [1-3]. It mostly affects previously healthy children, between 3 and 15 years of age, with a median age of around 6 years old and a slight predominance in males [1-3]. The term “FIRES” was proposed in 2010, and it is currently classified as a sub-type of new-onset refractory status epilepticus (NORSE) [1,3]. NORSE typically affects adults, may not be preceded by fever, and has an identifiable cause in about 50% of cases, including a specific viral infection or an autoimmune syndrome [2,4]. In FIRES, infectious, structural, toxic, and metabolic studies are usually normal, making it difficult to identify an etiology for this catastrophic condition [2,5].

FIRES is characterized by recurrent seizures or refractory status epilepticus preceded by febrile infection, such as a common upper respiratory tract infection or gastrointestinal infection [2,3]. Seizures typically begin after a period of low-grade fever, occurring 24 hours to 2 weeks before, with or without fever at the onset of the status epilepticus [1,4,6]. The clinical course is typically biphasic [1]. In the acute phase, seizures are brief at first, gradually increasing in frequency, and refractory status epilepticus is established within hours to days [1]. The chronic phase follows when status epilepticus stops, without a silent period between the two phases [1,5]. In this phase, seizures mostly occur every 2 to 4 weeks and patients show memory decline, speech impairment, functional disability, and emotional instability [1].

A continuous electroencephalogram (cEEG) should be performed as soon as possible to identify non-convulsive status epilepticus [1]. In FIRES, seizures are typically focal to bilateral tonic-clonic, with eye and head deviation and chewing movements, and epileptic foci are often frontal and temporal [1,2].

There are no specific treatment guidelines for FIRES [7-9]. However, FIRES has recently been categorized as an immune-inflammatory-mediated epileptic encephalopathy, since intrathecal overproduction of pro-inflammatory cytokines with known pro-convulsive activity has been reported [2,10]. In fact, anesthetic drugs are frequently required in combination with anti-seizure medications for seizure control, and other treatment strategies have been increasingly used, including a ketogenic diet (KD), intravenous (IV)
steroids, intravenous immunoglobulin (IVIG), plasmapheresis, and immunomodulatory agents (anakinra, tocilizumab, rituximab, tacrolimus, and cyclophosphamide) [1,2,4,8].

Despite treatment, clinical outcomes are disappointing and the general mortality rate is up to 20% to 25% [5,8]. Refractory epilepsy during long-term follow-up may be present in 90% of cases and severe intellectual disability in up to 38% [1,5,8]. Fortunately, children with FIRES only experience status epilepticus once [1]. We report a clinical case of a child with FIRES, in which a prompt, aggressive, and combined treatment approach led to a favorable outcome.

A previously healthy 6-year-old boy, with an unremarkable family history, was admitted to the pediatric emergency department due to repeated episodes of impaired consciousness, fixed gaze, perioral cyanosis, and drooling, with no involuntary movements. He had a recent history of low-grade fever and neck pain for three days, being afebrile for 24 hours. He had no other symptoms. Trauma and toxic ingestion were not reported. Non-contrast enhanced brain computed tomography was normal, and a cerebrospinal fluid (CSF) study disclosed mild pleocytosis (37 leukocytes/μL), a protein level of 0.54 g/L, and normal glucose. Worsening of the neurological status was observed, with no recovered consciousness between seizures, despite IV diazepam. Midazolam was started, and he was admitted to the pediatric intensive care unit (PICU), requiring invasive mechanical ventilation. IV acyclovir and empirical antibiotic therapy with ceftriaxone and clindamycin were started. The initial EEG, under midazolam perfusion, showed no epileptiform activity.

On the third day of his PICU stay, clinical improvement was observed and he was transferred to the pediatric ward. However, the seizures became increasingly frequent and long, despite levetiracetam and valproic acid administration, and 3 days later he developed status epilepticus and was readmitted to the PICU, with the diagnosis of FIRES. At this time, the cEEG showed criteria for status epilepticus, with temporal and frontal activity. He maintained clinical and electrographic seizures (mostly focal but sometimes generalized), without a complete recovery of normal behavior between them. Multiple anti-seizure medications were tried, in variable combinations: levetiracetam (up to 30 mg/kg per day), valproic acid (up to 40 mg/kg per day), lacosamide (up to 5 mg/kg per day), perampanel (4 mg once a day), and phenytoin (up to 10 mg/kg per day). Midazolam and ketamine infusions and propofol boluses were also administered.

Considering the diagnosis of FIRES, an additional treatment strategy was implemented (Table 1): methylprednisolone (30 mg/kg per day; for 5 days, starting on day 6), plasmapheresis (five sessions on alternate days; starting on day 8), enteric KD (starting on day 10), IVIG (2 g/kg divided between days 17 and 18), subcutaneous anakinra (4 mg/kg per day; starting on day 17), IV pyridoxine (50 mg twice a day; starting on day 17), and cannabidiol (20 mg/kg per day; starting on day 18). A barbiturate coma was also induced with thiopental for 48 hours (days 14 to 16). The patient was under invasive mechanical ventilation from days 10 to 25, and he completed 10 days of clindamycin, 15 days of acyclovir, 22 days of ceftriaxone, and 21 days of ciprofloxacin.

An extensive etiological investigation disclosed normal results.

Table 1. Timing of therapeutic strategies

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<th>D1</th>
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D, day; M, month; +, present treatment; IVIG, intravenous immunoglobulin.
Infectious causes were excluded. Oligoclonal bands were absent both in CSF and serum. Immunological studies were negative, including autoimmune encephalitis antibodies (antineuronal, anti-N-methyl-D-aspartate receptor, anti-aquaporin 4, anti-myelin oligodendrocyte glycoprotein, anti-voltage-gated potassium channel, anti-gamma aminobutyric acid-B, anti-a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, anti-glutamic acid decarboxylase-65, and anti-dipeptidyl-peptidase-like-protein-6). Contrast-enhanced brain magnetic resonance imaging (MRI) was normal.

Clinical and electrographic seizures gradually ceased from day 18 and status epilepticus ended on day 22, with cEEG showing temporal and frontal sporadic epileptiform discharges. He was transferred to the pediatric ward on day 30, under valproic acid, lacosamide, perampanel, phenytion, cannabidiol, pyridoxine, anakinra, and KD. At this time, he had periods of emotional instability, with progressive improvement, and was discharged on day 43.

An improvement in mood stability was observed after cannabidiol discontinuation. After 12 months of follow-up, the patient is functional in daily activities, remains seizure-free, and is slowly weaning from anti-seizure medications (currently on valproic acid, lacosamide, and clobazam). The last EEG showed slow activity excess in posterior areas (probably in relation to cannabidiol) and no evidence of epileptiform activity. Contrast-enhanced brain MRI was repeated and was also normal. He was recently diagnosed with attention deficit hyperactivity disorder and has mild cognitive impairment. Table 1 summarizes the timing of our therapeutic approach.

In our case, early aggressive and combined treatment was performed, without progression to refractory epileptic encephalopathy in the chronic phase. This outcome is remarkably atypical in FIRES patients, and it may be related to the adopted treatment strategy, in which drugs with anti-inflammatory and immunomodulatory central nervous system effects were promptly used.

As a type of immune-inflammatory-mediated epileptic encephalopathy, in over 50% of FIRES patients, the CSF features mild inflammatory changes with pleocytosis, and protein levels may be increased, without evidence of an infection or a specific autoimmune antibody, as in our patient. [1] According to this pathophysiology, conventional anti-seizure medications are largely unsuccessful in the acute phase [2,4]. Continuous IV anesthetic drugs, such as barbiturates, can momentarily stop seizure activity, which can return as soon as they are discontinued [4]. Interestingly, the anti-inflammatory properties of KD and cannabidiol seem to play an important role in FIRES treatment in the acute and chronic phases [4,8]. Early administration of KD—within the 1st week—is recommended [8]. Ketone bodies, namely β-hydroxybutyrate, inhibit the proteolytic activity of caspase-1, reducing the release of biologically active interleukin 1β (IL-1β), exerting an anti-inflammatory effect [8]. Similarly, cannabidiol features anti-inflammatory component and has been efficaciously used in treatment of refractory epileptic syndromes [1,4]. Anakinra is a recombinant version of a human IL-1 receptor antagonist that exerts the biological actions of IL-1β [4,10]. In drug-resistant epilepsy, such as FIRES, an increased expression of IL-1β in microglia and astrocytes is observed [4,10]. Studies support anakinra as a potential immunomodulator for patients with FIRES that should be considered within the first 2 weeks of presentation if seizures remain refractory after empiric treatment with IV steroids and IVIG, as in our case [2,4,8,10].

FIRES is an extremely rare neurological emergency with a challenging treatment approach and a difficult prognosis. Guidelines are urgently needed and should be focused on the early use of drugs with anti-inflammatory and immunomodulatory central nervous system effects.

This study was approved by the Ethics Committee of São João University Hospital Center (No. 116_2021). Written informed consent was obtained from legal representative of patient.

Conflicts of interest

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

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Author contribution

Conceptualization: NSG and MS. Writing-original draft: NSG, CM, and MS. Writing-review & editing: NSG, CM, JF, RS, and MS.

References


New Daily Persistent Headache after COVID–19 Vaccination in an Adolescent Patient

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New daily persistent headache (NDPH), according to the International Classification of Headache Disorders-3 (ICHD-3), is a primary headache lasting >3 months for which patients remember the exact onset. Historical evidence supports the possibility of viral infections, including coronavirus disease 2019 (COVID-19), triggering a new onset of persistent headache [1]. A few cases of NDPH after COVID-19 have been documented in children and adults (Table 1) [2-4]. Similarly, although persistent headaches after vaccination against COVID-19 have been described, there is a paucity of literature on NDPH after COVID-19 vaccination [5,6]. Herein, we report a case of an adolescent patient diagnosed with NDPH after receiving a second dose of the BNT162b2 mRNA COVID-19 vaccine (Pfizer Inc., New York, NY, USA).

A previously healthy 14-year-old female soccer player visited Chungbuk National University Hospital because of persistent headaches that began 3 weeks prior to admission. The headaches began suddenly on the day the second dose of the BNT162b2 mRNA COVID-19 vaccine was received, and the patient described them as involving throbbing pain in the entire head. Continuous headaches persisted on a daily basis (numeric rating scale [NRS], 4/10). Severe headache attacks occurred four times per day (NRS, 7/10) and lasted from 30 minutes to 2 hours. The headaches were aggravated by movement, such as walking and riding in a vehicle. Severe and persistent headaches were progressive, interfered with daily activities, and did not improve with rescue drugs. The patient’s medical history revealed no previous head trauma, headaches, or neuropsychiatric conditions. There was no family history of primary or secondary headaches (Table 1).

During the first admission, which lasted 6 days, supportive care was provided with intravenous hydration and acetaminophen, as well as oral naproxen. No neurologic deficit was noted; however, the patient exhibited neck stiffness. No abnormal laboratory findings, including platelet counts and coagulation profiles, were noted. Antibody tests against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were positive for the spike (S) protein and negative for the nucleocapsid (N) protein. In general, the presence of SARS-CoV-2 S antibody along with the absence of SARS-CoV-2 N antibody occurs when antibodies originate from vaccination. In contrast, the presence of both SARS-CoV-2 N and S antibodies usually implies prior infection with SARS-CoV-2. Upon discharge, persistent headaches continued, with an average NRS of 3/10 points,
but the frequency of severe attacks (NRS, 7/10) decreased to once daily.

The patient was re-admitted 5 weeks after headache onset due to persistent aggravating headaches. The frequency of severe headache attacks (NRS, 7/10) increased to three times daily and interrupted the patient's sleep. No neurologic deficit was noted. Brain magnetic resonance imaging with enhancement (T1- and T2-weighted scans) and all laboratory tests, including platelet count and coagulation profiles, showed normal findings. As headache control with rescue drugs was ineffective, the patient was prescribed topiramate (50 mg once daily) for headache prevention. For 2 months, the intensity of persistent headaches was slightly alleviated (NRS, 3/10), with once daily severe attacks (NRS, 5/10).

Four months after symptom onset, the patient was admitted because of worsening headaches after contracting COVID-19. The infection was confirmed by polymerase chain reaction. Persistent headaches worsened, even after the disappearance of systemic COVID-19 symptoms. Severe attacks (NRS, 7/10) occurred up to four times daily, and persistent pain was described as 3/10 on the NRS. Psychological evaluations were performed to evaluate the presence of comorbid psychiatric disorders and indicated that the patient had moderate levels of depression and hopelessness (Beck Depression Scale score, 22 points; Beck Hopelessness Scale score, 12 points; range for moderate depression, 21 to 30). However, we concluded that these conditions were not due to primary psychological problems, but the secondary result of severe physical pain. Topiramate was changed to valproic acid (500 mg once daily) and flunarizine (5 mg once daily).

Six months after symptom onset, the patient reported a decrease in severe attacks to once daily, as well as reduced persistent headaches, and she performed her usual daily activities without missing school. Nine months after symptom onset, the frequency and intensity of headaches further decreased. Since the patient reported headaches twice a week, flunarizine was discontinued. Two months later, the patient reported no headache at all, and valproic acid was discontinued. There were no further outpatient visits for 1 month after medication discontinuation.

Here, we report the first case of an adolescent patient diagnosed with NDPH after receiving a second dose of the COVID-19 vaccine, suggesting a unique cause of NDPH. We excluded secondary causes of headaches. In addition, medication-overuse headache was also considered a possible cause, but the overuse duration did not meet the eligibility criteria. In this patient, continuous headaches lasting >3 months fulfilled the ICHD-3 criteria for NDPH. Thus, we concluded that the COVID-19 vaccine may have caused these headaches.

Long COVID headache, which manifests with an unremitting and persistent character, can be similar to NDPH [7]. However, the distinction between long COVID headache and NDPH has yet to be explored. Our case implies the possibility of a relationship between vaccination against COVID-19 and NDPH. Taken together, headaches associated with the recent COVID-19 pandemic

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situation may provide a good opportunity to advance headache research, including on NDPH [7].

Identifying severe and persistent headaches and considering multiple causative factors, including vaccination, are of great importance. NDPH following vaccination has rarely been reported. However, an article specifically reported human papillomavirus vaccination as a trigger for NDPH [8]. Several hypotheses for the mechanism of post-vaccination headache have been suggested: SARS-CoV-2 S protein, the consequences of cytokine reaction by an imbalance in humoral and cellular immunity, and an innate immune reaction [6]. We expect that the additional monitoring of similar cases will elucidate the incidence and prognosis of chronic and severe headaches after COVID-19 vaccination in the pediatric population.

This study was approved by the Institutional Review Board (IRB) of Chungbuk National University Hospital (IRB No. 2022-04-001). Informed written consent for the publication of this report was obtained from both the patient and the legitimate guardian.

Conflicts of interest

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

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Conceptualization: HW and JKL. Data curation: JKL. Writing-original draft: HW. Writing-review & editing: JSK, WSK, and JKL.

References

A Case of Status Epilepticus Caused by Intravenous Tramadol

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Tramadol is a recently developed, centrally acting synthetic analgesic agent. The pharmacological mechanism of tramadol has not yet been fully elucidated, but unlike standard opioid analgesics, tramadol alleviates pain by modulating norepinephrine secretion and inhibiting serotonin reuptake [1]. The potency of tramadol is between 10% and 25% of that of morphine at the μ-opioid receptor, so it is considered a “weak opioid.” For this reason, it is regarded as relatively safe. Tramadol has been commonly used for postoperative pain treatment in children who have mild to moderate pain. The recommended dose for the intravenous (IV) route for children is 2 mg/kg every 4 to 6 hours, which is best for analgesic action with minimal side effects [2].

However, tramadol has some unique properties compared to other standard opioid medications that are attributable to its mechanism of inhibiting monoamine reuptake. Examples of the adverse effects of tramadol include respiratory depression, seizure, tachycardia, hypertension, serotonin syndrome, and manic syndrome [3].

Seizures have been noted as a concerning side effect of tramadol since its market approval in the United States in 1995, based on post-marketing reports to the U.S. Food and Drug Administration (FDA). Between 1997 and 2017, 30,730 tramadol-related cases had been reported to the FDA’s Adverse Event Reporting System, and seizures accounted for 7% of the cases [4].

The FDA issued a black-box warning in 2017, banning the use of tramadol in children and adolescents under the age of 12, and in those aged 12 to 18 with underlying diseases, due to its potential to cause serious respiratory side effects and death [5]. Despite the FDA’s warning, tramadol continues to be given, which is worrisome.

Here, we present a case of tramadol-induced status epilepticus in a 15-year-old girl with no past history of seizures. A 15-year-old girl (height, 159 cm; weight, 47 kg) presented to the emergency department due to abdominal pain. She had normal developmental milestones and her past medical history was unremarkable. She had undergone laparoscopic left ovarian cystectomy (pathology: functional cyst) 23 days earlier. A clinical examination revealed normal hemodynamic variables, and there was no sign of dehydration, or fever. On physical examination, widespread abdominal tenderness without rebound tenderness was found, while other physical examination and lab test results were normal. Abdominopelvic computed tomography (CT) showed paralytic small bowel ileus. She was referred to the gynecology department for conservative management. The patient was given 30 mg of IV ketorolac tromethamine (Trolac, Whanin Pharm Co, Seoul, Korea) and 100 mg of IV tramadol (Tandol, AJU Pharm Co, Seoul, Korea). Since the pain persisted, IV tramadol was
administered at intervals of 2 hours, shorter than the recommended interval, totaling 200 mg. About 1 hour after the second dose of IV tramadol administration, she developed a symmetric and generalized tonic seizure. The seizure lasted for 20 minutes and was suppressed with 4 mg of IV lorazepam. After approximately 13 hours, a focal tonic seizure of the right hand and leg with impaired awareness developed. The seizure was immediately suppressed with an additional administration of IV lorazepam, and she was referred to the pediatric neurology department for further management.

On the 2nd day of hospitalization, at 8:00 AM, a tonic seizure of both arms was observed and IV phenobarbital loading (20 mg/kg) was started. In order to rule out intracranial hemorrhage or any intracranial lesion, brain CT and brain magnetic resonance imaging (MRI) were performed and the results showed no abnormalities. An electroencephalogram (EEG) was performed and demonstrated slow background activity with theta bursts of 6 to 7 Hz sharp waves over the left hemisphere (Fig. 1A). At 4:00 PM on the same day, another tonic seizure of both arms was observed and IV fosphenytoin loading (20 mg phenytoin [PE]/kg) was started.

Fig. 1. Electroencephalogram characteristics of the patient. (A) It shows slow background activity with theta bursts of 6 to 7 Hz sharp waves over the left hemisphere. (B, C) These demonstrated reduction of the theta burst, suppressed background activity.
midnight, the patient woke up disoriented with crying, and she calmed down after 30 minutes. On the 3rd day of hospitalization, she first reported light headache and dizziness, followed by a generalized tonic-clonic seizure with vocalization. IV valproate was added. On the 5th day of hospitalization, a follow-up EEG was obtained and did not document significant changes. At 4:00 PM on the 6th day of hospitalization, the patient had a paroxysmal attack and cried out sharply while being emotionally distressed, agitated, and cognitively disoriented. Additionally, aggressive behaviors and impaired speech were observed. The event lasted for 20 minutes and was suppressed with 4 mg of IV lorazepam. IV phenobarbital and IV fosphenytoin were discontinued because of their unconfirmed effectiveness. At midnight on the 8th day of hospitalization, she developed a symmetric and generalized tonic seizure that lasted for 20 minutes, and IV fosphenytoin half-loading (10 mg PE/kg) was added again. The patient was given multiple antiseizure medications: lorazepam, phenobarbital, fosphenytoin, and valproic acid (Fig. 2). Follow-up EEG showed progressive reduction of theta bursts and suppressed background activity (Fig. 1B and C). On the 9th day of hospitalization, she showed no seizures and IV fosphenytoin was stopped. The patient was fully oriented and awake, and no further seizures or paroxysmal activities were noted. On the 13th day of hospitalization, she was discharged without any neurologic sequelae, and oral valproic acid was continued for an additional 4-week period. In the outpatient clinic, the patient exhibited normal EEG results after the discontinuation of valproic acid. No seizure was reported during 6 months of follow-up.

The patient’s legal caregiver provided written informed consent for the publication of the patient’s clinical details and other related information. This study was approved by the Institutional Review Board (IRB) of Daejin Medical Center (IRB No. 2023-01-006).

Seizures are a side effect of tramadol. This epileptogenic effect of tramadol occurs at both low and high doses [6]. The Adverse Drug Reactions Advisory Committee reported that tramadol can cause seizures, and using other drugs that lower the convulsive threshold concurrently could increase the likelihood of convulsions [7]. It is thought that the combination of injections at shorter-than-recommended intervals and the concurrent use of ketorolac may have exacerbated the side effects.

Talaie et al. [6] studied 61 patients with tramadol-induced seizures and reported normal results of EEG and CT scans of the brain in most patients. Our patient had normal results of brain CT and MRI, but abnormal EEG results. These abnormalities gradually decreased over time, and an EEG performed in the outpatient clinic returned to normal.

More problematically, the interpretation of repeated seizures despite discontinuing tramadol use and poor response to anti-seizure medication (ASM) remains. The patient was treated with multiple ASMs, but there was no prompt resolution of the seizures, and convulsive events repeated for 8 days. Further research on this pattern is deemed necessary.

In 2017, the FDA issued a black-box warning against the use of tramadol in children; however, there remains a population of children who continue to receive tramadol. In line with previous studies, the current case study suggests that a therapeutic dose of tramadol can induce seizures and even cause status epilepticus. Careful consideration is required when administering tramadol to adolescents.

Conflicts of interest

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

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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, brief communications, reviews, letters to the editor, and editorials. 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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**Manuscript preparation**

1. **General principles**

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

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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 at which the work was performed; (4) acknowledgement of research support; (5) name, address, telephone, fax number, and e-mail address of the corresponding author; (6) a running title should be written of 10 words or less.

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

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척수성 근위축증(SMA)에 허가받은
최초의 유전자 대체 치료제입니다.  

번아웃 진단과 치료를 통해,
SMA 환아들에게
건강한 삶을 선사할 수 있습니다.

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A New Paradigm of Immunoglobulin Injection

I.V.-Globulin SN inj. 10%

- Convenience
- High concentration immunoglobulin
- Reduced volume load
- Reduced infusion time

High Concentration I.V.-Globulin SN inj. 10%
- Routine EEG
- Portable EEG
- ICU Monitoring EEG
- Ambulatory EEG

- Wireless EEG
- Sleep (PSG)
- 64 – 256Ch HD EEG
- Animal EEG, Research

NATUS EEG/EMU/PSG
- Small and Light, Compact Design
- 128 / 256 Referential & 16 Differential Channels
- Max. 16,000Hz Sampling Rate for Research
- Sleep Study (PSG, 16Ch DC & Pulse Oximeter)
- Digital Switch Matrix for Functional Brain Mapping with Cortical Stimulator Interface
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- Base Unit compatible with Wireless / Ambulatory (Max. 30 mins)
- USB and Ethernet connection
- Dual Stream Recording for fast clinical review
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BESA® BESA Research Software
- Source Analysis & Imaging, Coherence, Time-Frequency Analysis
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하루, 한번

큐덱시서방캡슐은 *Topiramate* 서방형 제제입니다.¹

- **국내 최초의 Topiramate 서방형 제제입니다.¹**
- **복약편의성을 개선한 Topiramate 서방형 제제입니다.²**
- **FDA 허가를 받은 Topiramate 서방형 제제입니다.³**

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**Qudexy XR** (Topiramate) extended-release capsules

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References:

3. Qudexy XR FDA Prescribing Information (revised 03/29/2017), Reference ID: 4257003