














Clinical and Imaging Findings of Neonatal Seizures Presenting as Diffuse Cerebral White Matter Abnormality on Diffusion-Weighted Imaging without any Structural or Metabolic Etiology

확산강조영상에서 미만성 대뇌 백질의 이상을 보이는
 신생아 경련 환자에서 구조적 이상이나 대사와 관련된
 원인이 없을 경우 임상적 소견과 영상 소견의 특징

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Purpose Some patients with neonatal seizures show diffuse, symmetric diffusion-restricted lesions in the cerebral white matter. The aim of this study was to describe clinical and imaging findings of patients with neonatal seizures who had diffuse, symmetric diffusion-restricted lesions without any structural or metabolic etiology.

Materials and Methods A total of 56 neonates aged less than 1 week underwent brain magnetic resonance imaging (MRI) for evaluation of seizures from November 2008 to February 2017. After excluding 43 patients, 13 patients showed diffuse white matter abnormality on diffusion-weighted imaging. Initial and follow-up clinical and MRI findings were analyzed retro-

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spectively.

Results All 13 patients were born at full term. Among the ten patients who underwent a stool test for viruses, six were positive for rotavirus and one for astrovirus. MRI revealed diffuse, symmetric diffusion-restricted lesions distributed along the cerebral white matter, thalami, and midbrain variably.

Conclusion Diffuse, symmetric diffusion-restricted lesions involving the cerebral white matter can be seen in patients with neonatal seizures without any structural or metabolic etiology. Rotavirus is commonly but not exclusively detected in these patients. Nevertheless, viral infection-associated encephalopathy should be considered for patients with characteristic clinical and MRI findings.

Index terms Infant; Newborn; Rotavirus; Diffusion Magnetic Resonance Imaging

INTRODUCTION

Seizures are one of the most frequent neurological disorders in neonates that affect term and preterm infants. Neonatal seizures may have various clinical courses from benign, self-limited disease to severe and fatal disorders that can develop neurological sequelae. Neonatal seizures can develop by various etiologies that may affect the central nervous system in either the perinatal or postnatal period, including hypoxic-ischemic encephalopathy, stroke, hypocalcemia, hypoglycemia, and infection of the central nervous system (1, 2).

Radiological evaluation is part of the comprehensive evaluation of the etiology of seizures or is used to determine prognosis in neonates with seizures (2). MRI may show either normal findings or major abnormalities according to the underlying disease, such as hypoxic-ischemic encephalopathy or neonatal stroke. The absence of major abnormal findings is correlated with a normal neurological outcome (3).

Diffuse white matter abnormality on diffusion-weighted imaging (DWI) has been previously reported in neonates with viral infections, such as rotavirus, human parechovirus, and enterovirus (4-6). Recently, several studies have reported selective white matter lesions with rotavirus infection, in South Korea (7-9). There is a strong association between rotavirus and bilateral diffusion restriction on DWI exclusively involving the white matter in the early neonatal period.

This study aimed to describe clinical and imaging findings of diffuse and symmetric white matter abnormality in neonatal seizure patients who had no structural or metabolic etiology.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board of our hospital, and requirement for informed consent was waived (IRB No. 05-2015-067).

SELECTION OF PATIENTS

We retrospectively searched for brain MRI scans in patients aged less than one-week old from our hospital information system. Then we selected MRI scans that were performed to evaluate the cause of neonatal seizures. A total of 56 neonates aged less than 1-week old un-

derwent brain MRI for evaluation of neonatal seizures between November 2008 and February 2017. A Total of 33 patients were excluded due to combined perinatal disease that can be associated with neonatal seizure; structural brain abnormality ($n = 12$), perinatal distress ($n = 9$), neonatal sepsis/infection ($n = 4$), congenital heart disease ($n = 3$), metabolic disturbance ($n = 1$), and other disease ($n = 4$). After excluding nine patients who had negative result on DWI and one patient who had multifocal localized abnormality on DWI, a total of 13 patients were included in the present study (Fig. 1).

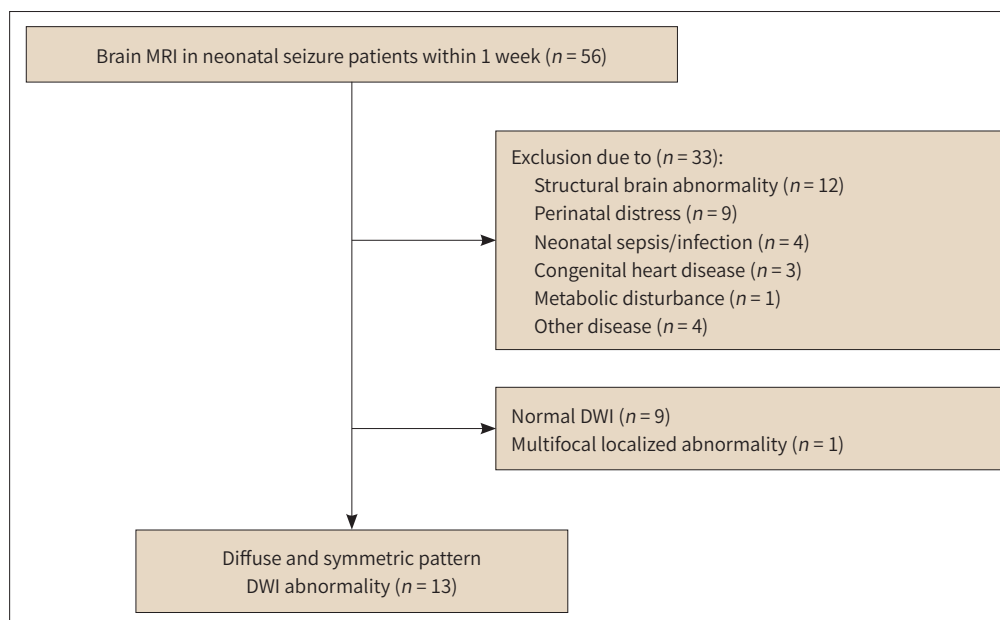
MRI PROTOCOLS

Among the 13 brain MRI scans, eight MRI examinations from our hospital were performed with the 3.0-T MRI machine (Skyra, Siemens, Erlangen, Germany) and three patients were examined on another 3.0-T (Vario, Siemens, Erlangen, Germany). Axial DWI was performed by using b-values of 0 and 1000 s/mm² followed by generation of an afferent diffusion coefficient (ADC) map. The remaining two patients underwent MRI at another hospital and the images were registered in our picture archiving and communication system.

CLINICAL, LABORATORY, AND NEUROLOGICAL FINDINGS

Clinical characteristics, including sex, age of onset, gestational age, body weight, month of hospital visit, presence of gastrointestinal symptoms and a stool viral test were reviewed. The stool viral test was performed by either a stool rotaviral antigen test by using an immunoassay technique or a multiplex polymerase chain reaction (PCR) test for human enteric adenovirus, group A rotavirus, norovirus, and astrovirus. Hospital visits between November and May were regarded as predilection season for the rotavirus. For evaluation of the central nervous system, characteristics of seizures, results of cerebral spinal fluid (CSF) analysis, and the dura-

Fig. 1. Flow diagram of the study population.



DWI = diffusion-weighted imaging

tion of hospital stay were recorded.

MRI ANALYSIS

MRI scans were retrospectively reviewed by two attending radiologists (one with six years of experience in interpretation of pediatric MRI and the other with five years of experience in interpretation of neuro-MRI) in a consensus session. Intervals between the onset of seizures and MRI scans were recorded. The areas with high signal intensity on DWI were reviewed, and ADC value was measured at cerebral white matter and corpus callosum, which were involved in every patient. Regions of interest (ROI) were measured on the ADC map by two readers (one with six years of experience in interpretation of pediatric MRI, and the other with two years of experience). For the accurate measurement, the image was magnified 200%, and circular ROI was drawn within the area of diffusion restriction. The diameter of circular ROI depended on the size of the lesion. The average measurement of the two readers was used for the analysis. Also, the presence of signal changes in white matter was reviewed. Axial T2-weighted image and fluid-attenuated inversion recovery (FLAIR) sequence, T1-inversion recovery, three-dimensional T1-weighted imaging (magnetization-prepared, 180-degree radio-frequency pulses and rapid gradient-echo) were reviewed to analyze signal change or structural abnormality, and susceptibility-weighted images or gradient-recalled echo images were analyzed to detect microhemorrhage. The microhemorrhage was defined as a dark signal focus on susceptibility-weighted imaging or gradient-recalled echo sequences.

FOLLOW-UP

The follow-up period was defined as the time interval between the onset of seizures and the last visit to the outpatient department. At the follow-up period, the presence of recurrent seizures after discharge, and presence of developmental delay were recorded. The developmental delay was assessed only in patients older than six months of age. If the follow-up MRI was available, presence of diffusion restriction, decrease in volume of cerebral white matter, high signal intensity of the involved white matter, and the degree of myelination were investigated. Completion of myelination was assessed according to a previously published table for age-specific progression of myelination on MRI (10).

STATISTICAL ANALYSIS

Descriptive statistics were used for description of age at the presentation of the seizure, hospital day, and ADC value at the areas with high signal intensity on DWI. A commercially available statistical software package was used for statistical analysis (Medcalc, version 12; Medcalc Software, Mariakerke, Belgium).

RESULTS

CLINICAL, LABORATORY, AND NEUROLOGICAL FINDINGS

Among total 13 patients, nine patients were males and four patients were females. Mean age was 5.1 ± 0.9 days (mean \pm standard deviation; range, 3–6 days). All patients were born at full term and body weight was adequate for gestational age, except for two patients who

weighed 2.3 kg. Eleven patients visited the hospital between November and May.

Two patients had gastrointestinal symptoms, including diarrhea and vomiting at the initial presentation or during hospitalization. 10 patients underwent stool viral test and 7 patients were positive for stool viral test. Six patients were positive for rotavirus (stool antigen test, $n = 1$; multiplex PCR test, $n = 4$; both, $n = 1$) and one patient was positive for astrovirus.

Nine patients showed generalized clonic seizures and four patients showed partial clonic seizures. Among the 10 patients who underwent a CSF analysis, all of them showed normal results. The mean time spent in hospital was 9.5 ± 3.5 days. When the seizure was observed during hospitalization, phenobarbital was administered to control the seizure.

MRI FINDINGS

MRI was performed at 2.4 ± 1.7 days (range, 0–5 days) after onset of seizures. MRI findings are summarized in Table 1. Diffusion restrictions were mainly distributed along the cerebral white matter tracks, corpus callosum, and involved thalami and midbrain variably. ADC values of cerebral white matter, and genu and splenium of the corpus callosum were 654.9 ± 79.2 , 570.4 ± 117.3 , and 582.0 ± 148.1 , respectively. In addition, symmetric posterior thalami involvement was observed in 11 patients (Fig. 2). Among them, all showed high signal inten-

Table 1. Summary of Laboratory, MRI, and Neurological Findings of Patients with Diffuse, Symmetric Diffusion Restricted Lesions

Case	Age (day)	Sex	Stool Viral Test	Seasonal Predilection*	GI Symptom	CSF Analysis	Diffusion Restriction Area	F/U MRI			Developmental Delay [†]
								Volume Loss	Cystic Change	PVWM Signal Change	
1	5	F	Rota	+	V, D	-	WM, CC, IC	N/A	N/A	N/A	N/A
2	6	F	Rota	+	-	-	WM, CC, IC, EC, AC, MB, VP	N/A	N/A	N/A	N/A
3	3	M	Rota	-	-	-	WM, CC, IC, EC, AC, PLT, MB	+	-	+	Motor
4	4	F	Rota	+	-	-	WM, CC, IC, EC	+	-	+	N/A
5	6	M	Rota	+	-	N/A	WM, CC, IC, EC, AC, PLT	+	-	+	-
6	5	M	Rota	+	D	N/A	WM, CC, EC, PLT	-	-	-	-
7	5	M	Astro	+	-	-	WM, CC, IC, AC, PLT, MB, VP	+	-	+	-
8	5	M	-	+	-	-	WM, CC, IC, EC, AC, PLT	N/A	N/A	N/A	-
9	5	F	-	+	-	-	WM, CC, IC, EC, AC, PLT	N/A	N/A	N/A	-
10	5	M	-	+	-	-	WM, CC, IC, EC, AC, MB, VP, PLT	N/A	N/A	N/A	N/A
11	6	M	N/A	-	-	-	WM, CC, IC, EC, MB, PLT	+	-	+	Language
12	6	M	N/A	+	-	-	WM, CC, IC, EC, MB, PLT	+	-	+	Language, Motor
13	5	M	N/A	+	-	N/A	WM, CC, IC, EC, AC, PLT	N/A	N/A	N/A	Language, motor

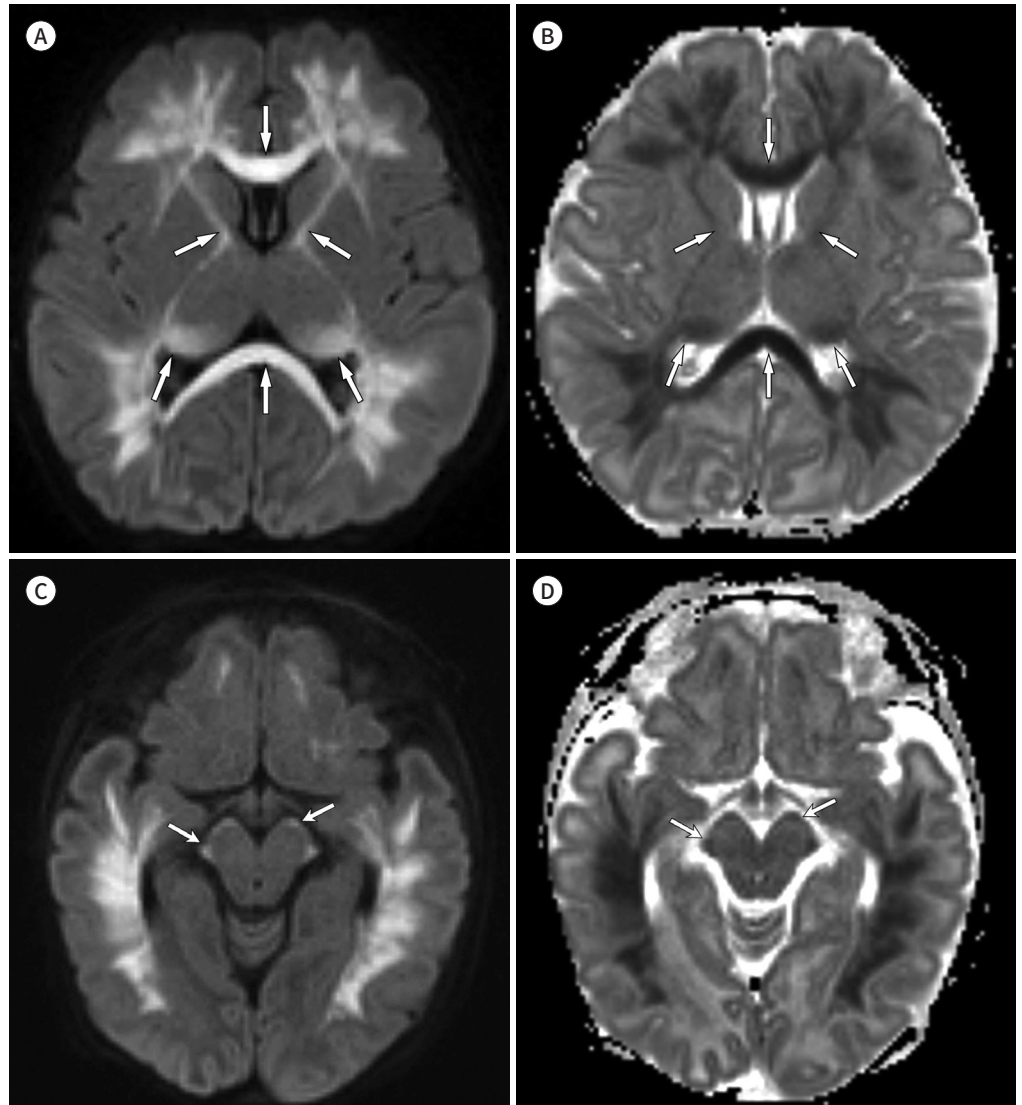
*Seasonal predilection positive means hospital visit between November and May.

[†] Developmental delay was assessed in patient older than 6 months old.

AC = anterior commissure, CC = corpus callosum, CSF = cerebrospinal fluid, D = diarrhea, EC = external capsule, F/U = follow-up, GI = gastrointestinal, IC = internal capsule, MB = midbrain, N/A = not available, PLT = pos-terolateral thalamus, PVWM = periventricular white matter, V = vomiting, VP = ventral pons, WM = cere-bral white matter

Fig. 2. Typical appearance of diffusion-restricted lesions of rotavirus-associated encephalopathy in a 6-day-old boy who presented with seizures.

A-D. Diffusion-weighted images (b-value = 1000 s/mm²) and apparent diffusion coefficients at the **(A and C)** levels of the corpus callosum and **(B and D)** midbrain show diffuse, symmetric diffusion-restricted lesions in the cerebral white matter tract, including the corpus callosum and internal capsule, posterior thalami, and basis pedunculi (arrows).



sity on either T2-weighted images or on the FLAIR sequence in the areas of diffusion restriction. Multiple foci of high signal intensity on T1-weighted images at the cerebral white matter that was affected on DWI were also observed. These multiple high signal intensity areas showed low signal intensity on T2-weighted images (Fig. 3). Neither microhemorrhage nor cystic change was detected on initial MRI scans.

FOLLOW-UP

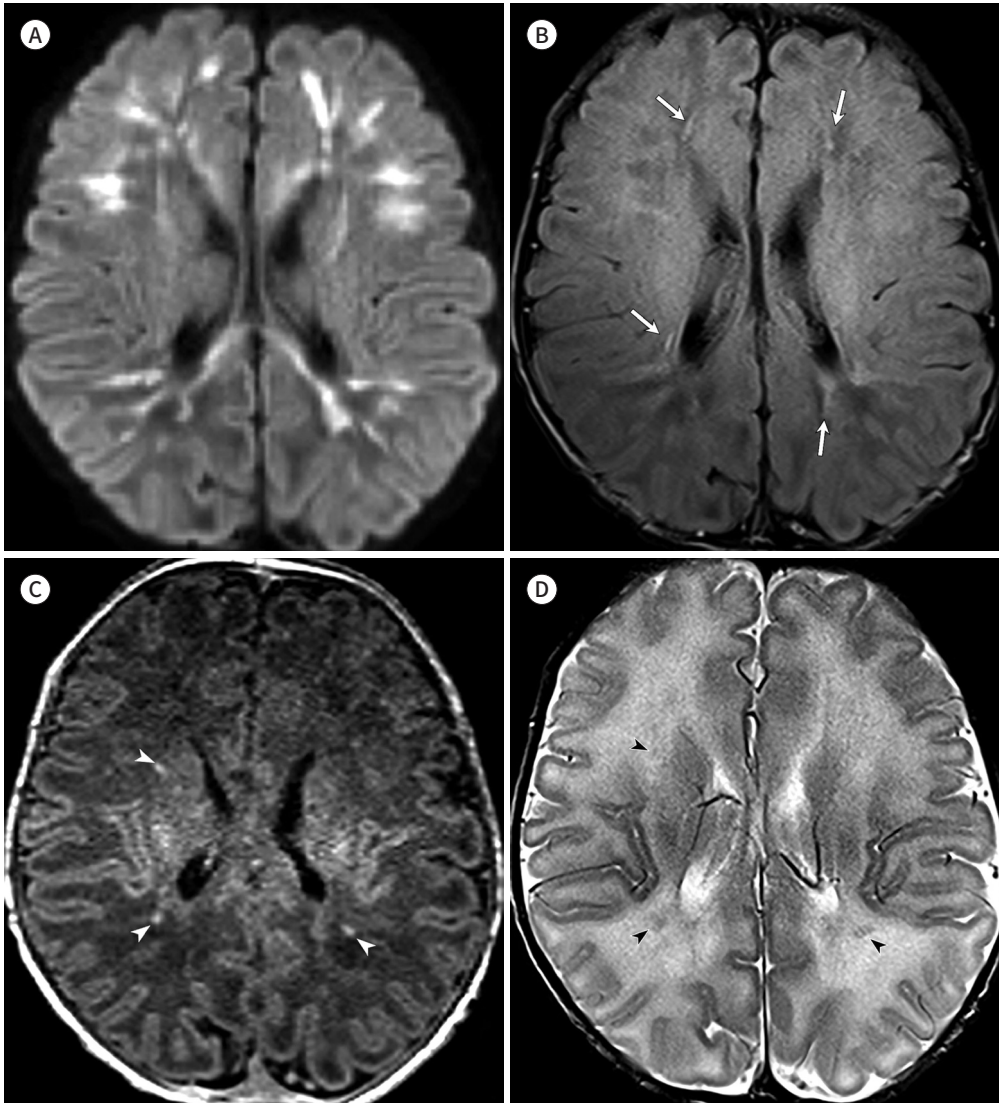
Out of 13 patients, 7 patients were followed up in pediatric outpatient clinics. The follow-up period was 7.1 ± 4.6 months (range, 3.7–13 months). No patients showed recurrent seizures after discharge. Two patients encountered language and motor delay, one had motor delay,

Fig. 3. Diffuse white matter injury in a 4-day-old boy with neonatal seizures. A stool test for viruses was negative in a multiplex polymerase chain reaction test.

A. A diffusion-weighted image (b-value = 1000 s/mm²) shows diffuse, symmetric high signal intensity involving the white matter tracts.

B. A fluid-attenuated inversion recovery image shows multifocal, curvilinear, high signal intensity in the periventricular and subcortical white matter (arrows).

C, D. T1- (magnetization prepared rapid gradient echo) (**C**) and T2-weighted (**D**) images show multifocal high and low signal intensities, respectively, in the cerebral white matter (arrowheads).



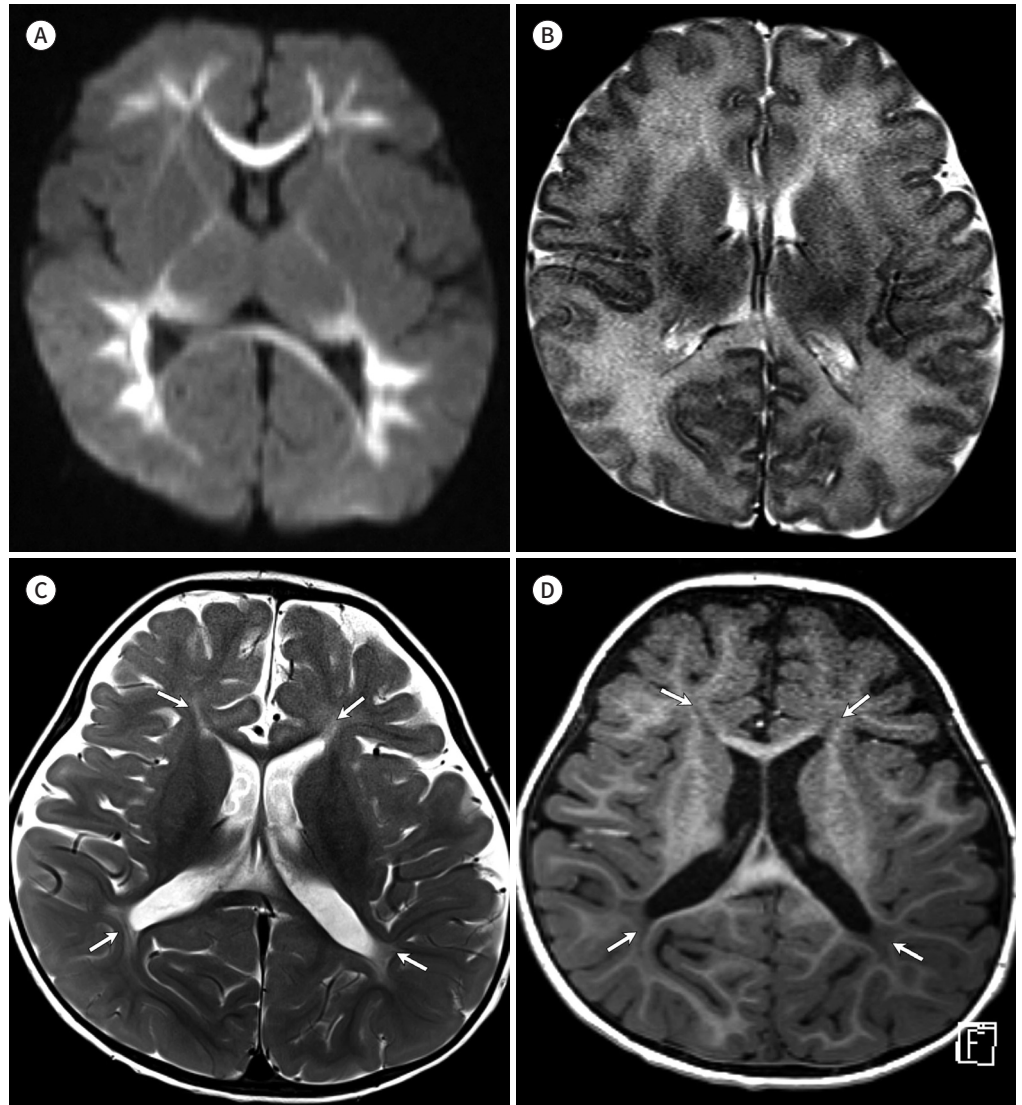
and one had language delay. None showed developmental delay.

Seven patients underwent follow-up MRI at the age of 8.1 ± 4.6 months (median, 6.6 months; range, 3.7–13.0 months). Five patients showed volume loss in cerebral white matter on both sides of the brain and four patients showed high signal intensity of the periventricular white matter on either T2-weighted images or FLAIR sequences (Fig. 4). Myelination delay was not observed on follow-up MRI.

Fig. 4. White matter volume loss in a 4-day-old boy with neonatal seizures and astrovirus infection. He had no perinatal hypoxic events.

A, B. Initial diffusion-weighted (**A**) and T2-weighted (**B**) images show characteristic diffusion-restricted lesions in the cerebral white matter tracts and posterior thalami. Note the normal white matter volume.

C, D. At the 13-month follow-up, T2- (**C**) and T1-weighted (magnetization prepared rapid gradient echo) (**D**) images show a decreased volume of the cerebral white matter, accompanied by T2 and T1 prolongation (arrows). His developmental status was within the normal range at the age of 13.1 months.



DISCUSSION

In our study, all patients who showed characteristic MR findings were full term babies and most of them showed adequate body weight. The gastrointestinal problem was presented only in three patients. Half of patients were positive for stool virus test but all of them were negative for any infection sign on CSF analysis. The seizure was single episode without recurrence, but white matter abnormality on follow-up MR and mild developmental delay may present in some patients.

Diffuse and symmetric diffusion restriction involving the cerebral white matter in neonatal

seizure patients was first described in patients with human parechovirus infection (4). MRI findings revealed excessive T2 high signal intensity in the cerebral white matter. Additionally, there was diffusion restriction in the white matter tracts, including the cerebral white matter, corpus callosum, internal capsules, and cerebral peduncles. Recent studies have also reported MRI findings of white matter injury in neonates with rotavirus infection in South Korea (7-9). The imaging findings of the above-mentioned studies were identical to those of our patients. Patients with diffuse cerebral white matter lesions tend to have more early-onset seizures between 4 and 6 days of life, and are positive for stool rotavirus antigen compared to patients without diffuse cerebral white matter abnormalities (7, 9). In these two studies, fever was hardly seen as a presenting symptom and only one patient showed positive PCR results for enterovirus RNA in the CSF. None of the patients were positive for rotavirus, enterovirus, or human parechovirus in the CSF and blood by PCR (7, 9). These previous findings are consistent with our patients.

In our study, interestingly, all of the patients who showed punctate T1-high and T2-low signal foci in the cerebral white matter showed diffusion restriction. These imaging findings are similar to those of MRI images in patients with white matter injury of prematurity, and they may show reactive gliosis, probably due to microglial activation (11, 12). These can be differentiated with microhemorrhage by using T2 star imaging or susceptibility-weighted images by less dark signal intensity of these imaging sequences. Eleven patients revealed diffusion restriction in the posterior thalami, also these lesions were symmetrical and specifically involved pulvinar. Although the exact mechanism of the thalamic lesions is not definite, we hypothesize that these lesions are contiguous with the diffusion restriction of various connection fibers from the visual cortex, premotor, prefrontal, and posterior parietal region (13).

Other finding that can be observed in white matter injury of prematurity, which is tissue loss of the white matter, was also seen in the follow up MRI at the late phase of the disease. This finding has also been reported in patients with either rotavirus or human parechovirus encephalitis (6-9). Cystic lesions appear from several days to several months after onset symptoms. This results in tissue loss several months later and it can be associated with an adverse neurologic outcome (6). However, the diagnosis of white matter injury of prematurity was not appropriate in our patients because all of them were full term and they did not have any perinatal hypoxic problems and metabolic events. In addition, MRI findings were not consistent with known MRI findings of hypoxic-ischemic encephalopathy in full-term neonates.

Rotavirus is one of the most important viral causes of gastroenteritis in children worldwide (14). The clinical manifestations of rotavirus infections include vomiting, diarrhea, fever, dehydration, and seizures. Seizures are the most common neurological complication of rotavirus, and the incidence of neurological complications is 2-3% in patients with rotavirus gastroenteritis (15, 16).

Brain MRI findings of rotavirus-associated encephalopathy have been reported anecdotally. A recent survey of rotavirus-associated encephalopathy in Japan (17) reported diffuse parenchymal swelling and areas of high signal intensity in the white matter, frontal-temporal cortex, and thalamus on T2-weighted or FLAIR images. They also reported diffusion restrictions in the splenium of the corpus callosum, subcortical area, and occipital-temporal white matter. Other studies reported asymmetric and focal or multifocal diffusion restriction involv-

ing cerebral white matter, dentate nucleus, cerebellum, or corpus callosum in patients with rotavirus-associated encephalopathy, which is different from our cases (18-20). Furthermore, the age of onset of the rotavirus-associated encephalopathy was older in these previous studies (17-20) than in our study, ranging from 18 months old to 4 years old.

Previous studies have reported a high prevalence of rotavirus infection ranging from 92.3% to 100% in patients with neonatal seizures and distinctive white matter injury (7-9). However, in our study, only six of 10 eligible patients were positive for rotavirus and one patient was positive for astrovirus. Although the number of patients in our study was small, rotavirus infection was less frequently detected in our study compared with other studies (7-9). Notably, three of 10 patients who underwent multiplex PCR tests showed negative results for human enteric adenovirus, Group A rotavirus, norovirus GI and GII, and astrovirus. Therefore, with regard to the high sensitivity of PCR tests for detecting rotavirus (21, 22), we would hypothesize that there might be viral infection other than rotavirus. Astrovirus can also cause neonatal gastroenteritis (23), but no reports have described neonatal encephalitis associated with neonatal seizures.

The pathophysiology of diffuse cerebral white matter injury in viral infection is not clear. Although direct invasion of the central nervous system is a possible mechanism of encephalopathy, an indirect effect of toxin-mediated injury has also been suggested (15, 16). Verboon-Maciolek et al. (24, 25) reported positive PCR results for rotavirus, enterovirus, and human parechovirus in the CSF or blood in patients with viral infection-associated encephalopathy (4, 5, 24, 25). However, recent reports have also shown that rotavirus was not detected in CSF studies (7) and normal CSF analysis (6-9). Although we did not perform PCR for rotavirus in CSF, there was no abnormality in CSF analysis among nine patients. These negative results of CSF analysis support an indirect effect of rotavirus on encephalopathy.

There are several limitations of the present study. First, this study was a retrospective study. Therefore, planning of radiological examinations, laboratory work-ups including stool PCR and CSF analysis, and clinical and imaging follow-up was not consistently performed. In addition, we performed stool PCR only to detect rotavirus, astrovirus, adenovirus, and norovirus. Because other viruses, such as enterovirus and human parechovirus, can cause similar encephalopathy in the neonate, we need to expand the spectrum of PCR examinations. Second, we could not determine a causal relationship between virus infection of the gastrointestinal tract and characteristic brain MRI findings. The last limitation of this study was too small number of patients to achieve adequate statistical power.

In conclusion, diffuse and symmetric diffusion restriction involving the cerebral white matter on MRI can be seen in patients with neonatal seizures without structural or metabolic etiology. Our study shows that rotavirus is commonly encountered, but not exclusively detected in these patients. Nevertheless, viral infection-associated encephalopathy should be suspected and DWI should be included in brain MR examinations in patients who present with neonatal seizures, even though there are no accompanying gastrointestinal symptoms.

Author Contributions

Conceptualization, H.J.; data curation, H.J., K.M., L.Y.J., K.Y.; formal analysis, H.J., K.M., Y.J.A., J.U.B.; investigation, H.J., K.M., Y.J.A., C.K.S., N.K.J.; methodology, H.J., K.M.; project administration, H.J.; resources, L.Y.J., B.S.Y., L.Y.; supervision, H.J.; validation, K.Y., J.U.B., C.K.S., N.K.J.; visualization,

H.J., K.M., R.S.N.S.; writing—original draft, H.J., K.M., R.S.N.S.; and writing—review & editing, H.J., K.M., R.S.N.S.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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확산강조영상에서 미만성 대뇌 백질의 이상을 보이는 신생아 경련 환자에서 구조적 이상이나 대사와 관련된 원인이 없을 경우 임상적 소견과 영상 소견의 특징

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목적 본 연구는 신생아 경련 환자에서 구조적 이상이나 대사로 인한 원인이 없으면서, 확산강조영상에서 미만성 대뇌 백질의 이상을 보이는 경우의 임상적 소견과 영상 소견의 특징을 기술하고자 한다.

대상과 방법 2008년 11월에서 2017년 2월 사이에 경련에 대한 평가를 위해 56명의 생후 1주 미만의 신생아가 뇌 자기공명영상을 시행하였다. 이중 33명을 제외한 23명중, 13명에서 확산강조영상에서 미만성 대뇌 백질 이상을 보였다. 내원 시 임상 소견, 자기공명영상 소견, 추적검사 결과에 대해 후향적으로 분석하였다.

결과 확산제한을 보인 13명의 환자는 모두 만기 분만 환자였다. 대변 바이러스 검사를 시행한 10명 중 6명은 로타바이러스, 한 명은 아스트로 바이러스가 검출되었다. 확산 제한은 대뇌 백질, 시상, 중뇌에 걸쳐 다양하게 분포하였다.

결론 신생아 경련 환자에서 구조적 이상이나 대사로 인한 원인이 없으면서, 확산강조영상에서 미만성 대뇌 백질의 이상을 보이는 경우, 로타바이러스가 검출되는 경우가 흔히 있었다. 따라서 이러한 임상적, 영상의학적 소견을 보일 때, 바이러스 감염과 관련된 뇌증의 가능성을 고려할 필요가 있을 것으로 판단된다.

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