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Neurodevelopmental outcomes in newborns with neonatal seizures caused by rotavirus-associated leukoencephalopathy

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ABSTRACT

Purpose: Rotavirus infection has recently been reported to be associated with seizures accompanied by leukoencephalopathy in newborns. We aimed to determine long-term outcomes and prognostic factors in newborns with neonatal seizures caused by rotavirus-associated leukoencephalopathy.
Methods: We retrospectively reviewed the records and brain magnetic resonance (MR) images of 32 patients who fulfilled the following criteria: (1) neonatal seizures, (2) distinctive symmetric cerebral white matter lesions on diffusion-weighted MR images (DWI), (3) rotavirus infection, (4) absence of a specific etiology of seizures, except for the aforementioned DWI lesions, and (5) Korean Bayley Scales of Infant Development II (K-BSID-II) assessment after 12 months of age.
Results: The mean age at seizure onset was 4.7 ± 0.8 days. The median age of the patients at the time of K-BSID-II assessment was 22 months. Fourteen patients (43.8%) showed normal or accelerated performance in the mental and motor scales, while 18 patients (56.2%) had delayed performance in the mental and/or motor scales. Seven patients (21.9%) had significantly delayed performances on the mental and/or motor scales. The percentage of volume of diffusion-restricted lesions based on total brain volume was significantly negatively correlated with the mental developmental index (MDI) score ($r = -0.507$, $p = .003$), but not with the psychomotor developmental index (PDI) score ($r = -0.324$, $p = .071$).
Conclusions: Rotavirus-associated leukoencephalopathy in newborns around 5 days of age can cause adverse neurodevelopmental outcomes with a wide range of severity. The extent of white matter lesion on initial DWI can predict neurocognitive outcome.

1. Introduction

Rotavirus is a well-known pathogen that causes gastroenteritis in infants and children. However, it can also cause a variety of central nervous system complications, such as convulsions with mild gastroenteritis [1–3], aseptic meningitis [4], encephalopathy with reversible splenial lesions [5–7], encephalitis [8,9], and cerebellitis [10]. Rotavirus infection has recently been reported to be associated with or to cause leukoencephalopathy in newborns presenting with neonatal seizures and distinctive pattern of restricted diffusion in symmetric cerebral white matter on magnetic resonance imaging (MRI) [11–14]. Newborns with rotavirus-associated leukoencephalopathy typically present with repetitive or clustered focal or multifocal clonic seizures at around 5 days of age accompanied by diffuse bilateral white matter and corpus callosum lesions on diffusion-weighted magnetic resonance imaging (DWI). The seizures usually occur after full-term births in patients without a history of perinatal asphyxia. This characteristic leukoencephalopathy in newborns does not seem to be exclusively associated with rotavirus infection. Human parechovirus- and enterovirus-infected infants also have similar MRI findings and clinical seizures [15–18].

Some of these newborns with rotavirus-associated leukoencephalopathy have serious cystic changes in cerebral white matter and decreased cerebral white matter volume in follow-up brain MRI [11–14]. However, until recently, there has been no research on the long-term prognoses of these infants using standard tests, although few small case series have described short-term outcomes [11,14]. We investigated neurodevelopmental outcomes in newborns with neonatal seizures caused by rotavirus-associated leukoencephalopathy using a standardized test. We also aimed to identify prognostic factors affecting outcomes of these patients.

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2. Methods

2.1. Patients

One-hundred and eight newborns were admitted to the neonatal intensive care unit at Ulsan University Hospital, which is a tertiary hospital located in Ulsan, Korea, between 2008 and 2014 with the chief complaint of seizures. All 108 patients underwent brain MRI, including DWI. One-hundred and seven patients underwent a stool rotavirus antigen test during their admission. Based on a retrospective review of electronic medical records, out of the 108 newborns, we first chose 56 patients who had rotavirus-associated leukoencephalopathy. Rotavirus-associated leukoencephalopathy was defined as follows: (1) seizures; (2) diffusion-restricted lesions in the diffuse symmetric cerebral white matter on DWI and no demonstrable cerebral cortical lesions or hemorrhages in the brain parenchyma or CSF spaces on MRI performed during the admission; (3) rotavirus infection; and (4) absence of a specific etiology of neonatal seizures, except for the aforementioned DWI lesions. The seizures in our study were defined as distinct phenomena witnessed and regarded as seizures by physicians or nurses and accompanied by definite abnormalities detected by using conventional electroencephalography, with frequent epileptiform discharges and discontinuous background patterns, and managed with anti-convulsive medications such as phenobarbital or phenytoin. We contacted each of the 56 patients' parents by telephone and mail to evaluate their long-term neurodevelopmental outcomes when they were older than 12 months. Thirty-three of the 56 patients visited our hospital and underwent the Korean Bayley Scales of Infant Development-II (K-BSID-II). One patient who was later diagnosed with Jacobsen syndrome was excluded. Thirty-two patients were included in the study. Of the 32 patients included in this study, 26 patients were included in two previous studies by our group [11,13]. Informed consent was obtained from all patients' parents. This study was approved by the institutional review board of Ulsan University Hospital.

2.2. MRI

MRI was performed on either a 3.0-T system (Intera Achieva; Philips, Best, Netherlands) or a 1.5-T system (Achieva; Philips). The protocol included T1-weighted imaging, T2-weighted imaging, fluid-attenuated inversion recovery imaging, and diffusion-weighted imaging with preparation of apparent diffusion coefficient maps. Initial MRI was performed within 3 days of seizure onset in all patients. Follow-up MRI was performed in 28 of the 32 patients (87.5%). Seventeen patients underwent MRI 3 months after seizure onset, 6 patients had MRI 4 months after onset, 3 patients underwent MRI 6 months after onset, 1 patient had MRI 2 months after onset, and 1 patient underwent 1 month after onset. Brain MR images from the patients were re-evaluated by two radiologists (one neuroradiologist with 16 years of professional experience [Y.C.W.] and one pediatric radiologist with 13 years of professional experience [S.H.C.]), who were blind to the clinical information and neurodevelopmental outcomes of these patients. Each radiologist independently reviewed the MR images at first. Then, the radiologists exchanged their opinions and reached a consensus on the MR image findings in subsequent meetings. To determine the extent of the white matter lesions in the initial MRI, the volumes of diffusion-restricted lesions on DWI and total brain volume (cerebrum, cerebellum, and brainstem) were measured in each patient using Aquarius iNtuition® (TeraRecon, Foster City, CA, USA) by a radiologist [S.H.C.]. The percentage of the volume of diffusion-restricted lesions was then calculated based on total brain volume ($Vol_{D/T}$). Thresholds appropriate for identifying diffusion-restricted lesions on the Aquarius iNtuition® were determined for each individual based on the radiologist's visual assessment.

2.3. Neurodevelopmental assessment using K-BSID-II

K-BSID-II consists of three subtests: the mental, psychomotor, and behavior rating scales [19,20]. We used the mental and psychomotor scales for this study. Raw scores on the mental and psychomotor scales were converted to a mental developmental index (MDI) and a psychomotor developmental index (PDI) score, which have normal distributions with means of 100 and standard deviations of 15. The K-BSID-II was administered by two trained testers over 45–60 min. The MDI and PDI scores were qualitatively classified using the following ranges: accelerated performance (115 and above), within normal limit (85–114), mild delayed performance (70–84), and significantly delayed performance (69 and below).

2.4. Prognostic factors

To analyze the associations between MR image findings and neurodevelopmental outcomes, the following measures on the initial DWI were investigated: (1) percentage of $Vol_{D/T}$ and (2) presence or absence of the involvement of thalamus, internal capsule, external capsule, brain stem, and caudate nucleus. Follow-up MR images were also evaluated for severity of atrophic changes in cerebral white matter and presence of cystic changes in cerebral white matter. Severity of atrophic change was classified as minimal, mild, moderate, or severe. To evaluate associations between clinical seizures and neurodevelopmental outcomes in our patients, we investigated the following factors: frequency of seizures, interval from first to last seizure, and presence of bradycardia (heart rate $<$100 beats per minute) during seizures.

2.5. Viral study

Immunochromatographic assays (Bioland Co., Ltd., Cheongwon-Gun, Korea in 2008–2010, and Asan Pharmaceutical, Seoul, Korea in 2011–2014) were performed to detect rotavirus antigen using stool samples in all 32 patients. Stool samples from 24 patients were subjected to reverse transcription polymerase chain reaction (RT-PCR) for the detection of enterovirus. CSF samples from 19 and 18 patients were subjected to PCR and RT-PCR to detect herpes simplex virus 1 and 2, and enterovirus, respectively. CSF samples collected from 11 patients were tested for rotavirus and human parechovirus using RT-PCR. All 32 patients underwent routine CSF analysis.

2.6. Statistical analysis

IBM SPSS Statistics 21 (IBM Corporation, Armonk, NY, USA) was used for the statistical analyses. Pearson correlation tests were used to analyze the relationships between MDI and PDI scores and the percentage of $Vol_{D/T}$. Kruskal-Wallis and Mann-Whitney *U* tests were used to compare differences in MDI and PDI scores according to variables other than the percentage of $Vol_{D/T}$. Scheffe's test was used for post-hoc comparisons when significant differences were detected. *P* values less than 0.05 were considered significant.

3. Results

3.1. Patient demographics

Twenty-one patients (65.6%) were male and 11 patients (34.4%) were female. Twenty-nine newborns (90.6%) were full-term and 3