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Original article

A nationwide survey of norovirus-associated encephalitis/encephalopathy in Japan

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Abstract

Background: Norovirus is a major pathogen of gastroenteritis and is known to cause encephalitis/encephalopathy. The aim of this national survey was to clarify the clinical features of norovirus-associated encephalitis/encephalopathy (NoVE) among children in Japan.

Methods: A nationwide survey of children with NoVE was conducted using a structured research form. The initial survey asked pediatricians about children with NoVE treated between January 2011 and March 2016. The second survey obtained patient information from two sources: hospitals that responded to the initial survey and those identified as having treated cases from a literature search.

Results: Clinical information was available for 29 children. Their median age was 2 y 8 m. The outcome was good in 13 patients and poor in 15. The interval between the onset of gastrointestinal symptoms and that of encephalitis/encephalopathy was significantly shorter in those with a poor outcome. At the onset of an elevated serum creatinine level and an abnormal blood glucose level were correlated with a poor outcome. Regarding the subtypes of encephalitis/encephalopathy, acute encephalopathy with biphasic seizures and late reduced diffusion and hemorrhagic shock and encephalopathy syndrome were frequent.

Conclusion: The outcome of children with NoVE was poor. Early onset of neurological symptoms, an elevated serum creatinine level, and an abnormal blood glucose level were associated with a poor outcome. No effective treatment was identified and this should be the subject of future studies.

Keywords: Acute encephalopathy; Creatinine; Blood glucose; Early onset; Outcome

Abbreviations: AESD, acute encephalopathy with biphasic seizure and late reduced diffusion; ANE, acute necrotizing encephalopathy; CSF, cerebrospinal fluid; HHV-6, human herpesvirus-6; HSES, hemorrhagic shock and encephalopathy syndrome; MERS, clinically mild encephalitis/encephalopathy with a reversible splenial lesion; NoV, norovirus; NoVE, norovirus-associated encephalitis/encephalopathy; PCPCS, pediatric cerebral performance category score; PCR, polymerase chain reaction

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1. Introduction

Norovirus (NoV) is one of the main causes of outbreaks of gastrointestinal infections, predominantly in winter. In Japan, several million people are thought to have NoV infections every year, although no precise data are available. NoV infection is usually characterized by a self-limited episode of nausea, vomiting, non-bloody diarrhea, and low-grade fever, lasting for a few days. Although deaths from NoV illness are rare, many children require hospitalization to treat dehydration.

Gastrointestinal infections may be complicated by central nervous system disorders, such as febrile seizures, gastroenteritis-related convulsions, and encephalitis/encephalopathy. Rotavirus infection is seen in approximately half of the children with gastroenteritis-related convulsions [1]. Rotavirus is the third most common pathogen in children with acute encephalitis/encephalopathy in Japan [2]. Kawamura et al. estimated that 21.6 children develop rotavirus-associated encephalitis/encephalopathy every year in Japan [3]. Several investigators have reported a relationship between NoV infection and gastroenteritis-related convulsions [4–6]. There have also been a few reports of children with acute encephalitis/encephalopathy associated with NoV infection [7–9]. However, the clinical features of NoV-associated encephalitis/encephalopathy (NoVE) remain unknown (Fig. 1).

Therefore, this study sought to clarify the clinical features of NoVE in children in Japan. We performed a nationwide survey of NoVE, including the symptoms, neuroimaging findings, and outcome. We also explored factors associated with a poor outcome in children with NoVE.

2. Patients and methods

We conducted a nationwide survey of NoVE in children in Japan. The study was approved by the Ethics Committee of Aichi Medical University. In this study, NoVE was defined as present in children with both a clinical diagnosis of acute encephalitis/encephalopathy, based on altered consciousness lasting for 24 h or longer with or without seizures, and virologically proven NoV infection.

The initial survey consisted of a brief structured questionnaire to determine the number of children with NoVE. Questionnaires were sent to board-certified pediatricians at 513 training hospitals approved by the Japanese Pediatric Society requesting information on the number of children with NoVE diagnosed between January 2011 and March 2016.

We also performed a search of the Japan Medical Abstracts Society database using the following search terms: (norovirus/TH or norovirus/AL), and (encephalitis/or encephalitis/AL) or (encephalopathy/TH or encephalopathy/AL). From the database search, we identified hospitals where children with NoVE were admitted between 2003 and 2016.

The second survey consisted of a structured research questionnaire. We obtained patient data from two different sources: hospitals that reported having children with NoVE in the initial survey and those identified as having treated children with NoVE from the literature search. In the second questionnaire survey, we asked for information on (1) the patient characteristics, including age, sex, pre-existing neurological disorders, and a history of febrile seizures; (2) the method used to diagnose NoV infection; (3) laboratory data, including the aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LD), creatinine kinase (CK), blood urea nitrogen (BUN), creatinine (Cr), sodium (Na), glucose (Glu), and bicarbonate (HCO_3^-) levels; (4) neuroradiological findings; (5) treatment; and (6) outcome. The outcome was evaluated using the pediatric cerebral performance category score (PCPCS). A good outcome was defined as the PCPCS of 1 or 2 at the last follow-up. A poor outcome was defined as the PCPCS of 3 to 6 at the last follow-up.

The subtypes of NoVE were classified based on the clinical course, neurological symptoms, and neuroradiological findings. Regarding the neuroradiological findings, the study group, which included an expert pediatric neurologist (AO), collected representative images and interpreted them. Table 1 shows the definitions of the four distinct subtypes of NoVE used in this study: acute encephalopathy with biphasic seizures and late reduced diffusion (AESD); hemorrhagic shock and encephalopathy syndrome (HSES); clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS); and acute necrotizing encephalopathy (ANE). The definitions of AESD, MERS, and ANE were adopted from previous studies [2,10–13] and were modified to fit this study. No definition of HSES has been established, and it differs among researchers [14–17]. We consider the main features of HSES to be rapidly worsening consciousness associated with multiorgan failure and marked brain edema. Patients who did not meet the definition of one of these four subtypes were categorized as "other".

We performed statistical analyses to determine the relationships between several variables and outcome. Each variable was compared between the patients with good and poor outcomes. We used Fisher's exact probability test and the Mann–Whitney U test to compare categorical and numerical variables, respectively. A p-value < 0.05 was considered to reflect statistical significance. All statistical analyses were performed using EZR ver. 1.33 (available at http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html).

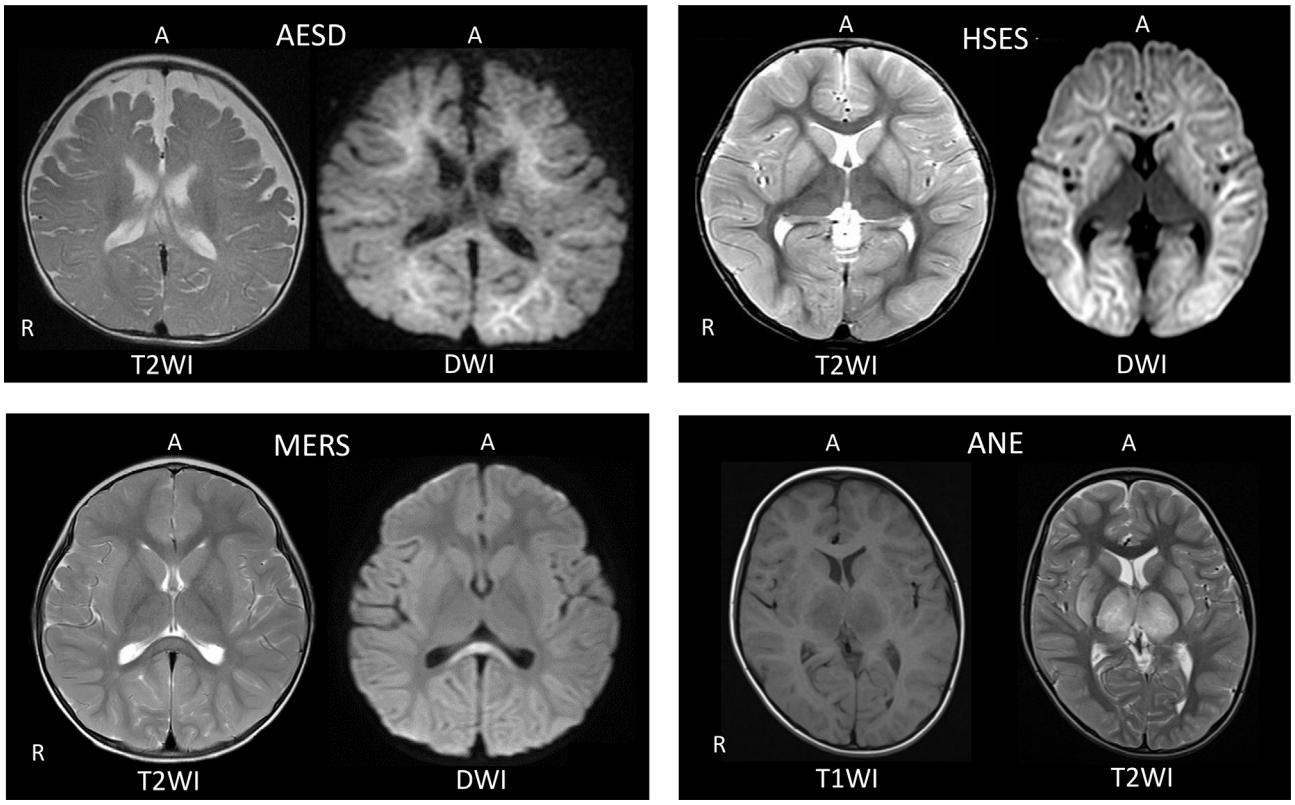

Fig. 1. Cranial MRI findings. A. Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) 3 days after the onset. The diffusion-weighted image (right) shows high signal intensities in the subcortical white matter and sparing around the Sylvian fissure bilaterally. B. Hemorrhagic shock and encephalopathy syndrome (HSES) 5 days after the onset. T2-weighted images (left) revealed marked edema predominant in cerebral cortex. Diffusion-weighted image (right) shows high signal intensities predominant in the subcortical white matter. C. Clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) the day after onset. T2-weighted (left) and diffusion-weighted (right) images show high signal intensities in the splenium of the corpus callosum. D. Acute necrotizing encephalopathy of childhood (ANE) 2 days after the onset. The T1-weighted image (left) shows low signal intensities in the bilateral thalami and basal ganglia. The T2-weighted image (right) shows high signal intensities in the same regions. T1WI, T1-weighted images; T2WI, T2-weighted images; DWI, diffusion-weighted images.

3. Results

A response to the initial questionnaire survey was obtained from 349 (67%) of the 513 hospitals. Within the survey period, 33 children with NoVE were reported by 27 hospitals. An additional 12 children with NoVE were identified from the database search. Therefore, 45 children were the subjects of the second questionnaire survey.

The attending pediatricians of 36 children responded to the second questionnaire survey, while no information on nine children was available because there was no response. Seven children were excluded from the analyses because four had profound underlying diseases (severe combined immune deficiency in two and mitochondria disease and carnitine deficiency in one each) and three were determined to have causes of encephalopathy other than NoV (hypoxic-ischemic encephalopathy, Wernicke's encephalopathy, and human herpesvirus-6 infection in one case each). As a result, the following analyses were performed on 29 children with NoVE.

Table 2 summarizes the patient characteristics. The median age was 2 y 8 m (range 4 m–12 y 6 m; SD 2y 7 m) and 21 patients were below three years of age. There were 10 boys and 19 girls. Five children had pre-existing neurological disorders (perinatal hypoxic-ischemic injury in two and hypoplasia of the corpus callosum, multiple congenital anomalies, and autism spectrum disorder in one each). These five children had delayed psychomotor development before the onset of NoVE. No history of febrile seizures was seen in any child. The symptoms were pyrexia in 20 patients, diarrhea in 20, and vomiting in 19. Shock was observed in 12. The median interval between the onset of gastrointestinal symptoms and that of encephalitis/encephalopathy was 1.5 (range 0–5) days. The neurological symptoms included impaired consciousness in all patients, seizures in 23, status epilepticus in 10, and delirious behavior in three.

To identify the NoV infection, a rapid antigen test was performed in 23 patients and was positive in 21. Polymerase chain reaction (PCR) of stool or vomit was performed in 15 patients and was positive in 13.

Table 1
Subtypes and definition of encephalitis/encephalopathy.

Subtypes of encephalitis/encephalopathy	All	Good outcome	Poor outcome
MERS	3	3	0
HSES	7	0	7
AESD	8	2	6
ANE	1	0	1
Others	10	8	1

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD)
1. Onset with convulsion (status epilepticus convulsivus in most cases)
2. Subsequent, transient improvement in consciousness.
3. Recurrence of convulsions on the fourth to sixth day of illness, followed by worsened consciousness.
4. Normal MRI on the first to second day of illness.
5. High signal intensity lesions in the cerebral subcortical white matter on diffusion-weighted images on the third to ninth day of illness. T2-weighted and FLAIR images may show high signal intensities along U-fibers.

Hemorrhagic shock and encephalopathy syndrome (HSES)
1. Rapid and severe impairment of consciousness.
2. Shock, multiorgan failure, and disseminated intravascular coagulation.
3. Diffuse brain edema on CT and/or MRI.
4. All these features appear within a day after the onset.
5. Exclusion of similar diseases such as AESD, ANE, Reye syndrome, heat stroke, overwhelming bacterial and viral infections, fulminant hepatitis, toxic shock, hemolytic uremic syndrome, and other toxin-induced disorders.

Clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS)
1. Onset with neuropsychiatric symptoms, such as abnormal behavior and mildly impaired consciousness.
2. Complete recovery without sequelae, mostly within ten days after the onset of neuropsychiatric symptoms.
3. High signal intensity lesion in the splenium of corpus callosum, in the acute stage. T1 and T2 signal changes are mild.
4. Lesion may involve the entire corpus callosum and the cerebral white matter in a symmetric fashion.
5. Lesion disappears within a week, with neither residual signal changes nor atrophy.

Acute necrotizing encephalopathy of childhood (ANE)
1. Rapid deterioration of consciousness with or without convulsions.
2. No CSF pleocytosis. Increase in CSF protein commonly observed.
3. Symmetric, multifocal brain lesions. Involvement of the bilateral thalami. Lesions also common in the cerebralperiventricular white matter, internal capsule, putamen, upper brain stem tegmentum and cerebellar medulla.
4. Elevation of serum aminotransferases of variable degrees. No increase in blood ammonia.
5. Exclusion of similar diseases such as AESD, HSES, Reye syndrome, heat stroke, overwhelming bacterial and viral infections, and fulminant hepatitis, toxic shock, hemolytic uremic syndrome, and other toxin-induced disorders.

Table 2
Patients background and outcome.

	All N = 29	Good outcome N = 13	Poor outcome N = 15	
Age (y, mo) *	2.8 (0.4–12.6)	2.6 (0.6–12.6)	2.6 (0.4–6.11)	$p = 0.93$
Sex (M:F)	10:19	3:10	7:8	$p = 0.25$
Pre-existing neurological disorders	5/29 (17%)	0/13 (0%)	5/15 (33%)	$p = 0.039$
The interval from the onset of GI symptoms (days) *	1.5 (0–5) N = 27	2.6 (1–5) N = 13	0.6 (0–2) N = 14	$p = 0.00011$
General symptoms				
Pyrexia	20/29 (69%)	10/13 (77%)	9/15 (60%)	$p = 0.43$
Vomiting	20/29 (69%)	10/13 (77%)	9/15 (60%)	$p = 0.43$
Diarrhea	19/29 (66%)	10/13 (77%)	9/15 (60%)	$p = 0.43$
Shock	12/29 (41%)	2/13 (15%)	10/15 (67%)	$p = 0.0093$
Neurological symptoms				
Seizures	23/28 (82%)	9/13 (69%)	14/15 (93%)	$p = 0.15$
Status epilepticus	10/28 (36%)	1/13 (8%)	9/15 (60%)	$p = 0.01$
Delirious behavior	3/27 (11%)	2/12 (15%)	1/14 (7%)	$p = 0.58$
Treatment				
Steroid pulse	22/28 (79%)	9/13 (69%)	12/14 (71%)	$p = 0.38$
Immunoglobulin	11/28 (39%)	5/13 (38%)	6/15 (40%)	$p > 0.99$

FS: febrile seizures, GI: gastrointestinal.
* Values are show as median (range).

PCR of the serum was performed in five patients and was positive only in one. PCR of cerebrospinal fluid (CSF) was negative in all six patients from whom CSF samples were obtained. The NoV subtype was determined in nine patients; all had the GII genotype. Viral isolation from stool and CSF was performed in five patients and was positive in one in stool sample.

Table 3 summarizes the laboratory data at the onset of NoVE. Severe laboratory abnormalities were common: a platelet count < 50,000/μL was seen in 5, AST > 200 IU/L in 13, ALT > 200 IU/L in 10, LD > 500 IU/L in 18, CK > 500 IU/L in 7, BUN > 20 mg/dL in 9, Cr > 1 mg/dL in 3, Glu > 200 mg/dL in 5, Glu < 40 in 4, Na > 150 mEq/L in 9, and HCO_3^- < 22 mmol/L in 21. CSF analysis revealed a cell count >10/μL in two children. No patient had an increased CSF protein level.

Steroid pulse therapy was given to 22 patients and intravenous immunoglobulin to 11. Other treatments performed in some patients included therapeutic hypothermia, plasma exchange, vitamin supplementation, thrombomodulin, mannitol, edaravone, cyclosporine, and dextromethorphan. The outcome was good in 13 patients and poor in 15. Four patients died. The outcome was unknown in one patient who was transferred to another hospital. All five patients with pre-existing neurological disorders were judged as having poor outcomes because the psychomotor development was markedly worse after NoVE.

4. Comparison between patients with good and poor outcomes

Tables 2 and 3 include the results of the statistical analyses. There were no significant differences in age or sex between the patients with good and poor outcomes. Shock and status epilepticus were significantly more frequent in those with poor outcomes. The interval between the onset of gastrointestinal symptoms and that of encephalitis/encephalopathy was significantly shorter in those with poor outcomes (0.6 *vs.* 2.6 days, $P = 0.00011$). Regarding the laboratory data at the onset of NoVE, there were significant differences in AST, Cr, and abnormal Glu (<40 mg/dL or ≥200 mg/dL). Steroid pulse therapy or intravenous immunoglobulin was not correlated with outcome.

5. Subtypes of NoVE

Eight patients were classified as AESD, seven as HSES, three as MERS, and one as ANE. The remaining 10 patients were not classified into any of these subtypes of NoVE (Table 1).

The median age of the AESD patients was 17 (range 4–55) months. The median interval between the onset of gastrointestinal symptoms and that of encephalitis/encephalopathy was 1.5 (range 0–4) days. At the onset of AESD, status epilepticus was seen in two and shock in three. One patient had rhabdomyolysis before the onset of AESD. A biphasic clinical course, characterized

Table 3
Laboratory data at the onset of encephalitis/encephalopathy and outcome.

	All N = 29	Good outcome N = 13	Poor outcome N = 15	
PLT ($\times 10^3$/μL)	337 (77–713) N = 23	337 (77–509) N = 12	394 (124–713) N = 11	$p = 0.097$
AST (IU/L)	233 (17–2522) N = 24	244 (34–2522) N = 13	239 (17–1052) N = 11	$p = 0.022$
ALT (IU/L)	104 (9–1134) N = 24	116 (15–1134) N = 13	98 (9–326) N = 11	$p = 0.052$
LD (IU/L)	622 (176–4236) N = 24	655 (235–4236) N = 13	622 (176–1523) N = 11	$p = 0.087$
CK (IU/L)	4868 (57–104400) N = 23	4868 (57–104400) N = 12	906 (77–3460) N = 11	$p = 0.12$
BUN (mg/dL)	23.5 (6.3–158) N = 24	24.0 (6.3–158) N = 13	24.1 (7.7–42.7) N = 11	$p = 0.056$
Cr (mg/dL)	0.44 (0.05–1.81) N = 24	0.36 (0.05–1.81) N = 13	0.51 (0.31–0.75) N = 11	$p = 0.0017$
Na (mEq/L)	140 (123–175) N = 24	143 (126–175) N = 13	150 (123–162) N = 11	$p = 0.38$
HCO_3^- (mmol/L)	15.7 (3.6–27) N = 17	17.4 (5.4–27) N = 8	14.2 (3.6–17.9) N = 9	$p = 0.10$
Glu < 40 (mg/dL) or ≥200 (mg/dL)	10 (53%) N = 19	1 (9%) N = 11	8 (100%) N = 8	$p = 0.0001$

Values are shown as median (range).
PLT: platelet, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LD: lactate dehydrogenase, CK: creatinine kinase, BUN: blood urea nitrogen, Cr: creatinine, Glu: glucose.

by transient recovery of consciousness, followed by worsening of consciousness associated with clustering seizures, was observed in all patients. The outcome was poor in six patients: PCPCS 3 in one and PCPCS 4 in five.

The median age of the patients with HSES was 35 (range 6–83) months. The median interval between the onset of gastrointestinal symptoms and that of encephalitis/encephalopathy was 0.6 (range 0–2) days. At the onset of HSES, five patients had status epilepticus and all had shock, and renal dysfunction, metabolic acidosis, and hyper- or hypoglycemia were observed in all patients. During the clinical course, all patients had metabolic acidosis, disseminated intravascular coagulation, and multiorgan failure. The outcome was poor in all: three patients died within two days of the onset, PCPCS 4 in three, and PCPCS 5 in one.

The median age of the patients with MERS was 74 (range 31–150) months. The median interval between the onset of gastrointestinal symptoms and that of encephalitis/encephalopathy was 2 (range 1–3) days. One patient had seizures. No patient had status epilepticus or shock throughout the clinical course. No severe laboratory abnormalities were seen in any patient. The outcome was good in all patients.

The patient with ANE was four years old. The ANE developed six hours after the onset of gastrointestinal symptoms. The patient became delirious, followed by rapid worsening of consciousness and status epilepticus. Although the patient was treated with steroid pulse and intravenous immunoglobulin, the patient died of multiple organ failure three days later the onset of ANE.

Regarding the 10 patients who were not classified into these four subtypes, the outcome was good in eight, poor in one, and unknown in one. In the patients with good outcomes, the neuroimaging findings were normal in six. One patient had an abnormal signal intensity in the cerebellar hemispheres suggesting cerebellitis, and the other had multiple high-intensity areas in both cerebral hemispheres on T2-weighted images suggesting acute disseminated encephalomyelitis. No neuroimaging was performed in one patient with a poor outcome or the one with an unknown outcome who was transferred to a tertiary emergency center.

6. Discussion

Our first nationwide survey of NoVE among children in Japan obtained data on the clinical and neurological features of 29 patients. The majority of the patients with NoVE were younger than three years of age. Neurological symptoms appeared mostly within three days of the onset of gastrointestinal symptoms. Marked laboratory abnormalities were common after the onset of NoVE. AESD and HSES were the most frequent subtypes of NoVE and were associated with poor outcomes. An elevated serum creatinine level and abnormal blood glucose level at the onset were correlated with poor outcomes.

We identified 29 patients with NoVE during a 14-year period. Kawamura et al. estimated that the incidence of rotavirus-associated encephalitis/encephalopathy in Japan was approximately 21.6 cases/year [3]. The incidence of NoVE should be lower based on the annual number of NoV infections in Japan. According to the Ministry of Health, Labor and Welfare in Japan, more than one million people in Japan develop NoV infections annually. However, the number of patients is strongly believed to be underestimated. The rapid antigen test was not marketed until 2012, so NoV infection was difficult to prove virologically because of the limited availability of PCR or viral isolation tests. Even after 2012, the rapid antigen test is not always performed in children with gastrointestinal symptoms. In addition, some patients with NoVE are presumed to be left unreported, because it is unrealistic to expect all attending pediatricians to respond to questionnaire surveys. We believe that the true incidence of NoVE is difficult to determine based on our results.

In our study, the majority of the patients were infants and young children below three years of age, which suggests that infants and young children are at high risk of developing encephalitis/encephalopathy when NoV infection occurs, considering that NoV infection can occur at any age, including in adults [18,19].

Regarding the subtypes of encephalitis/encephalopathy, AESD and HSES were frequent in patients with NoVE, implying that NoV infection tends to cause these severe subtypes of encephalitis/encephalopathy, although the incidence of NoVE is presumed to be infrequent. The incidence of the subtypes of encephalitis/encephalopathy differs with the causative viruses. AESD is the most common subtype in patients with HHV-6-associated encephalopathy, whereas HSES is uncommon. MERS is the most common subtype in patients with rotavirus-associated encephalitis/encephalopathy and influenza-associated encephalopathy [2]. The different incidence of subtypes according to the viruses is difficult to explain and the cause is likely to be multifactorial, including patient genetic factors, the acute immune response of the host to the infection, the virulence of the viruses, and the maturation of the brain.

Our study suggested that the outcome will be poor in patients with NoVE. A majority of the patients died or survived with neurological sequelae. This may be partly explained by the fact that severe subtypes of encephalitis/encephalopathy (HSES and AESD) were dominant in patients with NoVE; 13 of the 15 patients with poor outcomes were classified into these two subtypes. Steroid pulse therapy and intravenous immunoglobulin did not improve the outcome of the patients in our study.

Novel treatments for AESD and HSES are necessary to improve the outcomes of patients with NoVE.

Several factors predicted a poor outcome in the patients with NoVE. Although the subtypes of encephalitis/encephalopathy were clearly correlated with the outcome, they are not always determined easily at the onset. Of note, magnetic resonance imaging (MRI) does not show abnormal findings in patients with AESD during the first few days after the onset [10,20]. Therefore, predictors of a poor outcome at the onset of NoVE will help clinicians to determine the intensity of treatment. Interestingly, a shorter interval between the onset of gastrointestinal symptoms and that of encephalitis/encephalopathy was strongly associated with a poor outcome. Intensive treatment should be considered in such patients. Among the laboratory parameters at the onset of NoVE, the serum creatinine level and an abnormal blood glucose level were strongly correlated with poor outcomes. These two variables are easily measured in most hospitals in Japan. Therefore, if the usefulness of these variables is established, they can be used clinically. The serum creatinine level indicates the presence of acute kidney injury, as a marker of multiorgan failure. Acute kidney injury worsens the outcome of patients with sepsis, trauma, burns, and after cardiothoracic surgery. Recent studies have proposed the concept of brain–kidney crosstalk, indicating that acute kidney injury predisposes to brain dysfunction by causing generalized inflammation, leading to increased permeability of the blood–brain barrier [21]. Therefore, it is logical that an elevated serum creatinine level was strongly correlated with a poor outcome. We believe that the abnormal blood glucose level is explained by metabolic derangement due to multiorgan dysfunction. There is accumulating evidence that both hypoglycemia and hyperglycemia are associated with a poor outcome in critically ill patients [22–26]. We believe that these three parameters – a shorter interval from the onset of gastrointestinal symptoms, an elevated serum creatinine level, and an abnormal blood glucose level – will be useful for predicting the outcome of patients with NoVE.

The pathogenesis of NoVE is insufficiently understood. PCR and virus isolation were negative in all CSF samples, although the number of samples was small. This suggests that direct invasion of the brain by NoV is unlikely. Interestingly, the NoV genotype was GII in all PCR-positive samples. A previous study revealed that the GII/4 genotype caused more severe disease than other NoV genotypes in young children with acute gastroenteritis due to primary infection [27]. Further studies need to clarify the relationship between NoVE and the genotypes of NoV. At present, the pathogenesis of encephalitis/encephalopathy is presumed to differ according to the subtype.

The strength of our study is that it covered all of Japan. There have been no other nationwide studies of NoVE in children. The central review of the neuroradiological findings is another strength of our study. As a result, the diagnosis of subtypes of NoVE was objective, based on the assessment of multiple interpreters.

Nevertheless, there are several limitations to our study. First, the results may have been influenced by the retrospective study design. The response rate to the initial questionnaire was poor. Moreover, as mentioned above, a virological examination was not always performed in patients with possible NoVE, especially in patients with milder clinical presentations. Therefore, the number of patients with NoVE is presumed to be underestimated and the severity of NoVE may be overestimated. Second, the number of patients was too small to perform multiple comparison tests. Our study showed that some clinical variables are correlated with a poor outcome in patients with NoVE based on univariate analyses. However, multivariate analyses are necessary to clarify the predictors of a poor outcome more clearly. A prospective study of more patients with NoVE is necessary to overcome these problems. The virological analysis was not sufficient in our study. PCR or viral isolation is the gold standard for confirming viral infection. The rapid antigen test is a useful screening test, but its diagnostic value has not been established [28–30]. At present, the sensitivity of rapid antigen tests is not always sufficient compared with that of PCR. To confirm the presence or absence of NoV infection, PCR should be performed.

In conclusion, NoVE had a poor prognosis compared with other forms of encephalopathy, and the HSES subtype was relatively common. There is no known effective treatment. When the neurological symptoms appear early, the risk of a poor prognosis will be high if there is a blood glucose abnormality or the renal function is deteriorating. Future studies should seek to develop effective treatment methods.

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Appendix A. Supplementary data

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