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Original Article

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

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Abstract

Background: Adenovirus is a major pathogen causing febrile illness among children. It may also cause acute encephalitis/encephalopathy. This study aimed to elucidate the clinical features of adenovirus-associated encephalitis/encephalopathy (AdVE) among children in Japan.

Methods: A nationwide survey of children with AdVE was conducted. An initial survey was distributed among pediatricians to obtain information about children with AdVE treated between January 2014 and March 2019. A second survey was used to obtain the clinical information of children with AdVE from hospitals that responded to the initial survey and those identified from a literature search of the reported cases. We collected demographic data and information about symptoms of infection, neurological symptoms, laboratory parameters, treatment, and outcomes. Outcomes were determined using the Pediatric Cerebral Performance Category Score.

Results: Clinical information was available for 23 children with a median age of 39 months. Two had preexisting neurological disorders and six had a history of febrile seizures. The outcome was good in 15 patients and poor in eight patients. Serum lactate dehydrogenase, glucose, and ammonia levels were higher among children with a poor outcome compared to those with a good outcome. Clinically mild encephalitis/encephalopathy with a reversible splenial lesion was the most common type (n = 8), followed by acute encephalopathy with biphasic seizures and late reduced diffusion (n = 7).

Conclusion: A prior history of febrile seizures was frequent in children with AdVE. Several different subtypes of acute encephalopathy were seen in children with AdVE, and the outcome was poor in those with acute encephalopathy with biphasic seizures and late reduced diffusion and hemorrhagic shock and encephalopathy syndrome. Elevated lactate dehydrogenase, glucose, and ammonia levels on admission were found to correlate with a poor outcome.

Keywords: Adenovirus; Acute encephalopathy; Children; Outcome

1. Introduction

Adenovirus (AdV) is a common virus that primarily affects infants and young children, causing febrile illnesses throughout the year. It mainly targets the upper

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respiratory tract, leading to conditions like pharyngitis, tonsillitis, otitis media, and pharyngoconjunctival fever. AdV can also cause multi-organ symptoms, such as gastroenteritis, keratoconjunctivitis, and hemorrhagic cystitis. While central nervous system disorders caused by AdV are rare, they can occur in children of any age. Clinical manifestations may be more severe in young infants and immunocompromised children, potentially leading to meningitis and encephalitis [1]. Schwartz et al. conducted a study on 48 immunocompetent children with AdV-associated central nervous system (CNS) disease. They found that in most children with CNS symptoms, AdV was not detected in the cerebrospinal fluid (CSF) but rather in the respiratory or gastrointestinal specimens [2].

There have been few reports on Adv-associated encephalitis/encephalopathy (AdVE). Its incidence remains unknown, and may vary between young children and adults. A study in Japan examined 665 children with acute encephalopathy and found that AdVE accounted for 2.8 % of the cases, ranking as the fifth most common pathogen [3]. Similar reports from other countries have indicated that AdVE accounts for 1–5 % of the acute encephalitis cases in children [2,4]. A few case reports of children with acute AdVE have also been documented [5]. However, the clinical features of AdVE are not yet fully understood.

This study aimed to elucidate the clinical manifestations of AdVE and identify the risk factors for a poor neurological outcome. We conducted a nationwide survey in Japan to gather information on clinical symptoms, neuroimaging findings, and outcomes of children with AdVE. We also analyzed the risk factors associated with adverse outcomes in children diagnosed with AdVE.

2. Patients and Methods

We conducted a nationwide survey in Japan focusing on children aged <15 years who were diagnosed with AdVE. The diagnosis of AdVE was based on the presence of impaired consciousness for ≥24 h, with or without convulsions, along with virologically confirmed AdV infection. Virological confirmation of AdV infection was defined as at least one positive rapid antigen detection test, polymerase chain reaction (PCR), or virus isolation. The Ethics Committee of Aichi Medical University approved this study.

Initially, a questionnaire was used to determine the number of children with AdVE. The questionnaires were distributed to pediatricians at 472 training facilities approved by the Japanese Pediatric Society, requesting information on children diagnosed with AdVE between January 2014 and March 2019. We also collected reports of AdVE cases from the Japan Medical Abstracts Society database for the period between 2007 and 2019. The search terms included (adenovirus/TH or adenovirus/AL) and (encephalitis/ALor encephalitis/AL) or (encephalopathy/TH or encephalopathy/AL). We identified the corresponding authors of the relevant studies, and requested their cooperation for the survey.

A second survey was conducted using a structured research questionnaire. We gathered clinical information from two sources: hospitals that responded to the initial survey and had encountered children with AdVE, and hospitals identified through the literature search that had reported cases of AdVE. In the second questionnaire survey, we collected the following information: (1) patient characteristics, including age, sex, pre-existing neurological disorders, and history of febrile seizures; (2) symptoms at onset and the method used for diagnosing AdV infection; (3) laboratory data, including platelet, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase (LD), creatinine kinase (CK), blood urea nitrogen (BUN), creatinine, glucose (Glu), sodium, pH, bicarbonate, and ammonia levels; (4) neurological findings; (5) treatment administered; and (6) outcome, evaluated based on the pediatric cerebral performance category score (PCPCS). A poor outcome was defined as a deterioration in PCPCS at the last follow-up compared to before the AdVE occurrence.

AdVE subtypes were categorized based on the clinical course, neurological symptoms, and neurological findings as follows (Supplementary Table 1): Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD); Hemorrhagic shock and encephalopathy syndrome (HSES). It is important to note that there is no established definition for HSES, but in this study, it was characterized by a rapid deterioration of consciousness, accompanied by multiorgan failure and significant brain edema; Clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS): Acute necrotizing encephalopathy (ANE). AESD, MERS, and ANE were defined based on previous reports [6–10]. Patients who did not fit into any of these four subtypes were categorized as "others."

We performed statistical analysis to examine the relationships between various variables and the outcome. Each variable was compared between patients with good and poor outcomes. Fisher's exact probability test and the Mann–Whitney *U* test were used for categorical and numerical variables, respectively. Additionally, a multiple linear regression analysis was performed to identify factors associated with a poor outcome. A p-value < 0.05 was considered statistically significant. The statistical analyses were performed using the EZR software (version 1.61; available at: https://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html) [11].

3. Results

The initial questionnaire was distributed to 472 hospitals, and 344 (67 %) hospitals responded. A total of 27 children with AdVE were identified during the study period, with 19 children reported through the initial survey and an additional eight children recruited from the database search. Among them, 23 children from 19 hospitals, whose attending pediatricians responded to the second questionnaire survey, met the diagnostic criteria for AdVE and were included.

Table 1 presents the background information of the patients. The sample included 13 males and 10 females, with a median age of 28 (range: 11–101) months and 15 children being under 36 months of age. Two children had pre-existing neurological disorders, one with delayed psychomotor development due to perinatal ischemic-hypoxic encephalopathy and another with epilepsy but no delay in psychomotor development. Six (26 %) children had a history of febrile seizures, while one child had self-limited infantile epilepsy. Prior to the onset of AdVE, the PCPCS was 1 for 22 children, while one child had a PCPCS of 3.

The symptoms of AdV infection included pyrexia, upper respiratory symptoms, gastrointestinal symptoms, and eye symptoms in 22, 10, six, and four children, respectively. The median interval between the onset of AdV infection symptoms and the appearance of neurological symptoms was 1 day (range: 0–6 days). At the onset of AdVE, all children displayed impaired consciousness, including 19 cases of seizures and 13 of status epilepticus. Additionally, seven children exhibited delirious behavior, while two children experienced shock.

For the confirmation of AdV infection, a rapid antigen test was performed in 18 children using pharyngeal swab samples in 14 cases, stool samples in two cases, and a combination in two cases. Positive results were obtained for 16 of these patients. AdV was detected through virus isolation in six children from either pharyngeal swab or stool specimens. PCR analysis of pharyngeal swab and CSF was conducted in one child. AdV-DNA was positive in pharyngeal swab, but was negative in CSF. The AdV subtype was determined in five children, with type 1 observed in two cases, type 2 in two cases, and type 5 in one case. Pyrexia with no

Table 1
Patients background and outcome.

	All (N = 23)	Good outcome (N = 15)	Poor outcome (N = 8)	P value
Age (months)*	28 (17–101)	29 (16–101)	19.5 (11–80)	0.081
Sex (M:F)	13:10	10:5	3:5	0.22
Pre-existing neurological disorders	1/23 (4 %)	0/15 (0 %)	1/8 (12 %)	>0.99
Past history of febrile seizures	6/22 (27 %)	3/15 (20 %)	3/7 (43 %)	0.33
PCPCS before AdVE				
1	22	15	7	0.35
3	1	0	1	
The interval from the onset of AdV infection symptoms (days) *	1 (0–6)	1 (0–6)	1 (0–3)	0.30
AdV infection symptoms				
Pyrexia	22/23 (95 %)	14/15 (93 %)	8/8 (100 %)	> 0.99
Upper respiratory symptoms	10/23 (43 %)	7/15 (46 %)	3/8 (37 %)	> 0.99
Gastrointestinal symptoms	6/23 (26 %)	6/15 (40 %)	0/8 (0 %)	0.059
Eye symptoms	4/23 (17 %)	4/15 (26 %)	0/8 (0 %)	0.10
Neurological symptoms at the onset of AdVE				
Seizures	19/23 (82 %)	11/15 (73 %)	8/8 (100 %)	0.26
Status epileptics	13/23 (56 %)	6/15 (40 %)	7/8 (87 %)	0.074
Delirious behavior	7/23 (30 %)	3/15 (20 %)	4/8 (50 %)	0.18
Shock at the onset of AdVE	2/23 (8 %)	0/15 (0 %)	2/8 (25 %)	0.11
Treatment				
Steroid pulse	14/22 (64 %)	8/15 (53 %)	6/7 (87 %)	0.19
Immunoglobulin	7/22 (32 %)	3/15 (20 %)	4/7 (57 %)	0.15
Hypothermia/normothermia	6/22 (27 %)	3/15 (20 %)	3/7 (43 %)	0.33
PCPCS at the last follow-up				
1	15	15	0	Not assessed
2	4	0	4	
3	1	0	1	
4	1	0	1	
6	2	0	2	

PCPCS: pediatric cerebral performance category score, AdV: adenovirus, AdVE: adenovirus-associated encephalitis/encephalopathy.
* Values are shown as median (range).

respiratory, eye, or gastrointestinal symptoms was observed in 4 children from whom AdV type 1 or type 2 was isolated. Pyrexia and gastrointestinal symptoms was recognized in 1 child from whom AdV type 5 was isolated.

Table 2 summarizes the laboratory data on admission to the hospitals that provided clinical information. Laboratory data were obtained on the day of the onset of AdVE in 16 children, on the second day in 2, on the third day in 1, on the fourth day in 1, on the fifth day in 1, and on the seventh day in 1. Laboratory data were not available for 1 child. In most children with AdVE, laboratory abnormalities were not significant. However, the following abnormalities were observed: LD > 400 U/L in five children, CK > 500 U/L in one child, BUN > 20 mg/dL in one child, Glu > 200 mg/dL in four children, ammonia > 200 μg/dL in two children, and acidosis (pH < 7.20) in three children based on blood gas analysis. CSF analysis was performed in 22 children, with two of them displaying CSF pleocytosis and elevated protein levels.

Information regarding treatment was available from 22 children (Table 1). Steroid pulse therapy was administered to 14 (63 %) children, while intravenous immunoglobulin was administered to seven (32 %) children. Hypothermia/normothermia treatment was performed in six children. Other optional treatments included hyperosmotic diuretics, vitamin cocktail treatment, free radical scavengers, thyrotropin-releasing hormone analogs, plasmapheresis, normothermia, and hyperbaric oxygen.

The outcome of AdVE was good in 15 children, while eight children had a poor outcome, including two children who died. Among children with a good outcome, PCPCS was 1 at the last follow-up. Among the children with a poor outcome, PCPCS was 2 in four children, 3 in one child, 4 in one child, and 6 in two children.

3.1. Comparison between patients with good and poor outcomes

Tables 1 and 2 show a comparison of the characteristics of children with good and poor outcomes. There were no significant differences in terms of age, sex, pre-existing neurological disorders, AdV infection symptoms, and neurological symptoms between the children with good and poor outcomes. However, the children with a poor outcome were generally younger and had a higher frequency of shock and status epilepticus. Conversely, gastrointestinal and eye symptoms were exclusively observed in children with a good outcome. Regarding laboratory data, serum LD, Glu, and ammonia levels were significantly higher in children with a poor outcome compared to those with a good outcome. The administration of steroid pulse therapy or intravenous immunoglobulin was not correlated with the outcome.

A multiple linear regression analysis was performed using serum LD, Glu, and ammonia levels as potential risk factors for a poor outcome. However, none of these factors showed a significant difference in their association with the outcome.

3.2. AdVE subtypes

Table 3 presents the subtypes of AdVE. Among the children included in the study, eight, seven, and two were classified as MERS, AESD, and HSES, respectively. None of the children met the criteria for ANE. Additionally, six children did not fit the criteria for any of these subtypes and were categorized as "others."

Among the eight children with MERS, the median age was 57.5 (range: 16–101) months. The median interval between the onset of AdV infection symptoms and the onset of AdVE was 2 (range: 1–5) days. Six of these

Table 2
Laboratory data on admission and outcome.

	All (N = 23)		Good outcome (N = 15)		Poor outcome (N = 8)		P value
PLT ($\times 10^3/\mu L$)	N = 22	279 (149–483)	N = 15	247 (149–364)	N = 7	318 (166–483)	0.066
AST (U/L)	N = 22	35.5 (23–238)	N = 15	34 (23–108)	N = 7	44 (32–238)	0.14
ALT (U/L)	N = 22	14.5 (7–93)	N = 15	16 (7–42)	N = 7	12 (7–93)	0.75
LD (U/L)	N = 22	304 (156–726)	N = 15	282 (156–726)	N = 7	418 (296–485)	0.0074
CK (U/L)	N = 21	73 (42–1644)	N = 14	71.5 (42–1644)	N = 7	85 (45–425)	> 0.99
BUN (mg/dL)	N = 22	9 (5.3–22.7)	N = 15	9 (5.3–22.7)	N = 7	9 (8–18)	0.65
Cr (mg/dL)	N = 22	0.29 (0.15–0.53)	N = 15	0.27 (0.15–0.51)	N = 7	0.31 (0.22–0.53)	0.11
Na (mEq/L)	N = 22	135 (126–140)	N = 15	135 (126–140)	N = 7	135 (131–140)	0.80
pH	N = 18	7.38 (6.80–7.45)	N = 12	7.38 (7.25–7.43)	N = 6	7.28 (6.80–7.45)	0.96
HCO_{3-} (mmol/L)	N = 18	20.2 (12.5–26.5)	N = 12	20.6 (12.5–26.5)	N = 6	19.1 (15.6–24.9)	0.68
Glu (mg/dL)	N = 18	114.5 (71–366)	N = 13	99 (71–228)	N = 5	248 (106–366)	0.0068
Ammonia (μg/dL)	N = 19	42 (10–242)	N = 13	36 (10–85)	N = 6	95 (31–242)	0.031

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.

Table 3
Subtypes of encephalitis/encephalopathy.

	MERS (N = 8)	AESD (N = 7)	HSES (N = 2)	Others (N = 6)
Age (months)	57.5 (16–101)	23 (13–50)	11 and 12	39 (18–80)
Sex (M:F)	5: 3	2: 5	1: 1	5: 1
The interval from the onset of AdV infection symptoms (days)	2 (1–5)	1 (0–3)	0 and 2	1.5 (0–6)
Neurological symptoms at the onset of AdVE				
Seizures	6	7	2	4
Status epileptics	1	7	1	4
Delirious behavior	3	2	1	1
Shock at the onset of AdVE	0	0	2	0
Poor outcome	0	5	2	1

AdV: adenovirus, MERS: clinically mild encephalitis/encephalopathy with a reversible splenial lesion, AESD: acute encephalopathy with biphasic seizures and late reduced diffusion, HSES: hemorrhagic shock and encephalopathy syndrome.

children experienced seizures, while one had status epilepticus. Delirious behavior was observed in three children. None of the children with MERS exhibited laboratory abnormalities or shock during the course of their illness, and all had a good outcome.

Among the seven children with AESD, the median age was 23 (range: 13–50) months. The median interval between the onset of AdV infection symptoms and the onset of AdVE was 1 day (range: 0–3 days). All children experienced status epilepticus, and two displayed delirious behavior. None of them developed shock, and a biphasic clinical course was observed in all cases. The outcome was poor in five of these children.

Among the two children with HSES, one was 11 months old and the other was 22 months old. The median interval between the onset of AdV infection symptoms and the onset of AdVE was 0 days and 2 days, respectively. At the onset of HSES, one child had status epilepticus, and both children experienced shock. Both children died.

Among the six children categorized as "others", five had a good outcome, while one had a poor outcome. Among the five patients with a good outcome, three exhibited normal neuroimaging findings, while one developed cerebellitis without any neurological sequelae.

4. Discussion

In our nationwide survey of AdVE among children, we analyzed the clinical features of 23 children with AdVE. The median age at AdVE onset was 28 months, and pre-existing neurological disorders were rare. However, a history of febrile seizures was present in 27 % of the children. The most common subtypes observed were MERS and AESD. Among the 23 patients, eight had a poor outcome, which was frequently associated with AESD and HSES. No specific clinical symptoms were correlated with a poor outcome. However, LD, Glu, and ammonia levels were higher in patients with a poor outcome compared to those with a good outcome.

The prevalence of AdVE in children has been relatively unclear and presumed to be low. Goto et al. conducted a nationwide survey of children with acute encephalopathy in Japan between 2005 and 2006, and identified 18 AdVE cases in 636 patients [3]. In our study, 23 children with AdVE were identified through the initial survey. Based on these findings, it is estimated that ≤10 children develop AdVE annually in Japan. Huang et al. reported that among 3,298 children with confirmed AdV infections, 109 developed central nervous system dysfunction, while 28 were diagnosed with encephalitis [12]. An epidemiological study conducted in Finland demonstrated that AdVE accounted for 5 % of the children with encephalitis [4]. Similarly, a report from SickKids in Toronto identified eight cases of encephalitis among 977 children with AdV infections [2]. Considering the large number of children with mild symptoms of AdV infection who are not tested for viral detection, the overall risk for AdVE among children appears to be low.

The age at onset of AdVE in our study was in agreement with previous reports, with two-third of the cases occurring in children <3 years old. In the SickKids report, four out of eight patients were younger than 3 years old [2]. Similarly, the study from Finland observed AdVE exclusively in children aged 1–3 and 4–6 years old [4]. As different AdV subtypes can cause primary infections at different ages, determining the exact age at primary infection is challenging. It is generally accepted that primary AdV infection occurs within the first 5 years of life in most children. Therefore, the age at onset of AdVE may be similar to the age of AdV infection without complications.

It is interesting to note that 27 % of the children with AdVE in our study had a history of febrile seizures. In Japan, the estimated rate of febrile seizures among children is 3.4–9.3 % according to the guidelines in Japan [13]. The rate of a history of febrile seizures was also high in children with influenza-associated encephalopathy. Our previous study showed that a prior history of

febrile seizures was present in 20 % of children with seasonal influenza-associated encephalopathy and in 30 % of children with 2009 pandemic flu-associated encephalopathy [14]. In contrast, no patients with norovirus-associated encephalopathy had a prior history of febrile seizures [15]. This suggests that fever sensitivity may be a predisposing factor for AdVE. Several studies have identified the variants of *SCN1A*, which is a major gene associated with Dravet syndrome characterized by pronounced fever sensitivity, in children with acute encephalopathy without a prior diagnosis of epilepsy [16,17]. This serves as an illustrative example of genetic predisposition to acute encephalopathy. At present, there have been no virus-specific studies of the genetic background of acute encephalopathy. The occurrence of AdVE may be related to genetic susceptibility, and the genetic background of children with AdVE will be an important area of investigation in future studies.

Among the 23 children with AdVE in our study, eight had a poor outcome. A nationwide survey of acute encephalopathy in Japan conducted between 2014 and 2017 reported a complete recovery rate of 57.7 %, neurological sequelae in 34.6 %, and a mortality rate of 4.7 % [18]. This suggests that the outcomes of AdVE may not differ significantly from the overall outcomes of acute encephalopathy. Although we did not find any clinical symptoms consistently related to a poor outcome in children with AdVE, status epilepticus and shock were relatively more common among those with a poor outcome. These factors may be associated with an unfavorable outcome, but due to the small number of patients in our study, we were unable to identify significant differences. Interestingly, gastrointestinal and eye symptoms were not observed in patients with a poor outcome. However, in the reports of Schwartz et al [2], 4 of 8 children with AdVE had diarrhea; Three of them had neurological sequelae. The differences in outcome may be explained by the variations in AdV subtypes, as the clinical manifestations of AdV infections are closely related to the causative AdV subtype [19,20]. AdV types 1, 2, 3, 4, 7, and 21 have been known as common pathogens of febrile respiratory illness; AdV types 8, 19, and 37 are related to keratoconjunctivitis; AdV types 40 and 41 have an affinity for gastrointestinal tract with gastroenteritis or diarrhea [19]. AdV type 7 has been reported to be sometimes isolated from extraneural sites in children with acute encephalopathy, especially associated with epidemic AdV type 7 pneumonia in children [20]. Analyzing the AdV subtypes involved in AdVE is necessary to clarify the relationship between AdVE outcomes and specific AdV subtypes.

In our study, we found that elevated LD, Glu, and ammonia levels on admission were correlated with the outcome of children with AdVE. These findings are consistent with previous reports. Kawano et al. reported that increased LD levels on admission were associated with a poor outcome in children with acute encephalopathy and encephalitis [21]. Azuma et al. found that maximum LD levels were a weak predictor of poor outcome in children with acute encephalopathy exhibiting a bright tree appearance on magnetic resonance imaging [22]. Elevated Glu levels have also been linked to a poor outcome in acute encephalopathy in children. Abnormal Glu levels at onset were correlated with a poor outcome in children with norovirus-associated encephalitis/encephalopathy [15]. Additionally, elevated Glu levels have been reported in children with AESD. Maeda et al. observed elevated ammonia levels in children with AESD [23]. Both Glu and ammonia levels are included in predictive scores for early AESD diagnosis [24–26]. These laboratory values are typically readily available in most hospitals, and can be useful for prognostication in children with acute encephalopathy, including AdVE.

In this study, we were able to determine the AdVE subtype in 17 of the 23 patients, with MERS being the most common subtype (n = 8), followed by AESD (n = 7). These findings were consistent with the results of nationwide surveys on acute encephalopathy in Japan [6,18], identifying MERS and AESD as the most common subtypes in children, while HSES is less frequently observed. Notably, HSES was observed in two children with AdVE. Previous nationwide surveys have reported that HSES accounted for 1.9 % and 1.7 % of the acute encephalopathy cases for the periods of April 2007–June 2010 [6] and April 2014–June 2017 [18], respectively. It is unknown whether HSES is more common in AdVE compared to acute encephalopathy caused by other viral infections. Reporting bias should also be taken into consideration, as patients with more severe clinical manifestations may be more likely to be reported than those with milder symptoms. As expected from previous studies, the outcome of AdVE was correlated with the AdVE subtype. All eight children with MERS had no neurological sequelae, while a majority of children with AESD or HSES had a poor outcome. The clinical features observed in each subtype were consistent with previous reports. Children with MERS tended to be relatively older in age, status epilepticus was observed in all children with AESD, and shock was observed in both children with HSES.

There were several limitations in this study. First, the number of patients was insufficient for adequate statistical analysis. When we could obtain information of more children with AdVE, the prognostic value of laboratory data could be established. Multivariate analysis should be performed to clarify the predictors of poor outcome. Second, the virological analysis was not sufficient in some children with AdVE. The rapid antigen test is useful for screening, but the type of AdV cannot be determined. PCR and/or virus isolation tests are needed to determine the type of AdV. There are many types of

AdV and the type of AdV will correlate with the clinical manifestations of AdV infection as well as the subtypes and outcome of AdVE. Detailed virological analysis of AdV is necessary to clarify the relationship between types of AdV and clinical manifestations of AdVE. Third, the timing of measuring laboratory data varied among patients, although a large majority of laboratory data in this study was obtained within the first 2 days after the onset of AdVE. This problem was difficult to avoid due to a retrospective design of the study. Prospective studies will be necessary to determine the prognostic value of laboratory data.

In summary, we presented clinical features of 23 children with AdVE. Clinical manifestations of AdVE varied among patients, and outcome was poor among those with AESD or HSES. Specific factors associated with a poor outcome could not be identified, although elevated LD, Glu, and ammonia levels were common among those with a poor outcome. Further studies with greater number of children with AdVE are required to understand the clinical manifestations and examine the risk factors for poor outcomes.

Author contributions

MN collected and analyzed data and wrote the first draft of the manuscript. AO, SA, MI, and TaS contributed to data curation. AO was responsible for the organization and coordination of the study, and data analysis. ToS supervised the study. All authors contributed to a critical review of the manuscript.

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CRediT Author Contribution Statement

Mika Nakazawa: Data curation, Investigation, Writing – original draft. **Shinpei Abe:** Data curation, Writing – review & editing. **Mitsuru Ikeno:** Data curation, Writing – review & editing. **Taiki Shima:** Data curation, Writing – review & editing. **Toshiaki Shimizu:** Data curation, Writing – review & editing. **Akihisa Okumura:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2023.10.002.

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