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(Citation)
Journal of the Neurological Sciences,469:123377

(Issue Date)
2025-02-15

(Resource Type)
journal article

(Version)
Version of Record

(URL)
https://hdl.handle.net/20.500.14094/0100492973

Journal of the Neurological Sciences 469 (2025) 123377

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Epidemiology and treatment trends for acute encephalopathy under the impact of SARS-CoV-2 pandemic based on a prospective multicenter consecutive case registry

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ARTICLE INFO

Keywords:
Acute encephalopathy
Influenza virus
Severe acute respiratory syndrome coronavirus 2
Targeted temperature management
High dose corticosteroid therapy
Pediatrics

ABSTRACT

Background: Acute encephalopathy is a severe condition predominantly affecting children with viral infections. The purpose of this study was to elucidate the epidemiology, treatment, and management of acute encephalopathy. The study also aimed to understand how the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has affected epidemiological trends.

Methods: This retrospective study used the database of the Febrile Acute Convulsion and Encephalopathy registry, a prospective multicenter consecutive case registry for acute encephalopathy and febrile convulsive status epilepticus. Pediatric patients aged 0–18 years hospitalized and diagnosed with acute encephalopathy between January 2020 and August 2023 were included in this study.

Results: Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) was the most common syndrome (36 cases, 27.5 %). SARS-CoV-2 was the most common pathogen (19 cases, 14.5 %), followed by influenza virus type A (15 cases, 11.5 %). Targeted temperature management was performed for 25 (69.4 %) of 36 patients with AESD; 5 (50.0 %) of 10 patients with hemorrhagic shock and encephalopathy; and only 1 (5.9 %) of 17 patients with mild encephalitis or encephalopathy with a reversible splenial lesion (MERS). High-dose corticosteroids were administered to 9 (90.0 %) of 10 patients with hemorrhagic shock and encephalopathy and 11 (30.6 %) of 36 patients with AESD.

Conclusions: The primary causative pathogen of acute encephalopathy has changed to SARS-CoV-2. AESD remains the most common syndrome. Targeted temperature management is more, whereas high-dose corticosteroid therapy is less, frequently used. No specific treatment for mild encephalitis or encephalopathy with a reversible splenial lesion has been established.

Abbreviations: AESD, Acute encephalopathy with biphasic seizures and late reduced diffusion; COVID-19, coronavirus disease 2019; EEG, electroencephalography; FACE, febrile acute convulsion and encephalopathy; FluA, influenza virus type A; HSES, hemorrhagic shock and encephalopathy; MERS, mild encephalitis/encephalopathy with a reversible splenial lesion; PCPC, Pediatric Cerebral Performance Category; RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TTM, targeted temperature management.

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https://doi.org/10.1016/j.jns.2024.123377
Received 26 September 2024; Received in revised form 11 December 2024; Accepted 31 December 2024
Available online 3 January 2025

1. Introduction

Acute encephalopathy is a severe condition that predominantly affects children, and it is characterized by a high incidence of neurological sequelae and a high mortality risk [1]. It is often secondary to viral infections, such as those caused by the influenza virus and human herpes virus 6/7. It also has an acute onset and presents with prolonged impaired consciousness. Its incidence is high in Asian countries, especially Japan, with approximately 500–900 cases reported annually [2].

Epidemiological studies on acute encephalopathy in Japan were conducted in 2010 [3] and 2017 [4] using nationwide surveys with questionnaires targeted at pediatric specialist training institutions. In these studies, the common age of onset, pathogens, and outcomes of acute encephalopathy syndrome were reported. Additionally, the Guidelines for the Diagnosis and Treatment of Acute Encephalopathy in Childhood 2016 (AE GL 2016) were published by the Japanese Society of Child Neurology [1]. In 2021, a web-based questionnaire survey targeting pediatric neurologists was conducted to evaluate changes in treatment before and after the publication of the AE GL 2016 [5]. It reported the treatment and management methods for acute encephalopathy syndromes and their changes over time. These studies have revealed much about the epidemiology and treatment practices for acute encephalopathy, which were previously unknown. However, they had limitations, including their retrospective design, recall bias, and incomplete response rates from eligible institutions or physicians.

Furthermore, there have been significant global changes due to the spread of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) since 2020. In Japan, the first case of COVID-19 was confirmed in January 2020. Thereafter, waves of the pandemic began. Since the emergence of the omicron variant in Japan in January 2022, the number of pediatric patients infected by SARS-CoV-2 has increased [6]. Changes in the proportions of causative pathogens relative to those reported by previous studies have been observed, which may influence the epidemiology of acute encephalopathy.

This study aimed to elucidate the epidemiology, treatment, and management of these acute encephalopathy. It also aimed to investigate how the COVID-19 pandemic has changed epidemiological trends.

2. Materials and methods

2.1. Ethics

All the methods adhered to the principles of the Declaration of Helsinki. The study design, including the use of the prospective registry, was approved by the ethics committee of Kobe University Graduate School of Medicine (No. 180011). The requirement for informed consent was waived because of the retrospective nature of the analysis of the anonymized information.

2.2. Study design and patients

This retrospective study used the Febrile Acute Convulsion and Encephalopathy (FACE) registry, a prospective multicenter consecutive case registry for acute encephalopathy and febrile convulsive status epilepticus. Enrollment into the FACE registry began in January 2020. By August 2023, the FACE registry included nine participating facilities in Japan, including four tertiary care hospitals with pediatric intensive care units, two tertiary care hospitals with intensive care units, two secondary care hospitals with intensive care units, and one secondary care hospital without intensive care units. The FACE registry included pediatric patients who met the following criteria: (1) definitive diagnosis with acute encephalopathy or (2) admission for febrile convulsive status epilepticus lasting 30 min or longer or altered consciousness lasting 6 h or longer. Pediatric patients aged 0–18 years who were hospitalized and diagnosed with acute encephalopathy between January 2020 and August 2023 were included in this study.

2.3. Observation items and definitions

Acute encephalopathy and acute encephalopathy syndrome were diagnosed according to guidelines and previous reports [1,7,8]. Briefly, we defined acute encephalopathy as follows: (1) acute onset during the course of an infectious disease, (2) consciousness disturbance lasting for at least 24 h, and (3) exclusion of other diseases such as encephalitis and meningitis. The sequelae were assessed using the Pediatric Cerebral Performance Category (PCPC) scale [9]. An increase by one or more points in the PCPC score from pre-hospitalization to one month after discharge represented the presence of sequelae. We investigated specific therapies for acute encephalopathy, including targeted temperature management (TTM), high-dose corticosteroids, vitamin administration, immunoglobulin therapy, free radical scavengers, osmotherapy, cyclosporine, and blood purification therapy. We also assessed the performance of continuous electroencephalography (EEG) monitoring. The decision to perform these treatments or management was left to the discretion of each clinician at each hospital.

TTM included hypothermia and normothermia therapies, which aim to lower the core body temperature to a target of 34–36 °C. TTM is typically performed for 24–72 h using a surface-cooling blanket. For high-dose corticosteroid therapy, methylprednisolone was administered at 30 mg/kg (maximum 1000 mg) for 3 days, followed by gradual tapering. Vitamin therapy typically involves the administration of vitamins B1, B6, C, E, L-carnitine, biotin, and/or coenzyme Q10 for approximately 10 days. The administration of free radical scavengers was achieved by administering edaravone. Osmotherapy involved the administration of mannitol or glycerol. Continuous EEG monitoring was conducted using electrodes placed according to the International 10–20 system. However, continuous EEG monitoring is performed in most cases with a reduced number of electrodes, such as using four channels (bilateral frontal and occipital regions).

2.4. Statistical analysis

The data are expressed as numbers (%) or medians (interquartile ranges). We compared the differences in patient characteristics and treatments among the three major acute encephalopathy syndromes. For the comparison of the three groups, we performed statistical analyses using the Kruskal-Wallis test to compare continuous dependent variables and the Fisher's exact test to compare categorical variables. For items that demonstrated a significant difference, post hoc pairwise comparisons between individual groups were conducted exploratorily using either the Mann-Whitney test or Fisher's exact test. EZR version 1.41 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) was used for analysis, and p-values of <0.05 denoted statistical significance.

3. Results

Of 845 patients enrolled in the FACE registry between January 2020 and August 2023, 136 were diagnosed with acute encephalopathy or encephalitis. After excluding two cases of limbic encephalitis, one case of posterior reversible encephalopathy syndrome, and two cases of meningitis, 131 patients were diagnosed with acute encephalopathy.

3.1. Characteristics of the patients

The characteristics of the patients diagnosed with acute encephalopathy are shown in Table 1. The median age was 33 months, but most of the children were 1 year old (36 cases, 27.4 %) (Fig. 1). Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) was the most common syndrome (36 cases, 27.5 %), followed by clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) (17 cases, 13 %) and hemorrhagic shock and encephalopathy

Table 1
Characteristics of the patients.

Sex, male, n (%)		70 (53.4)
Age, months [IQR]		33 [17.5, 180]
Pre PCPC	1	105 (80.2)
	2	10 (7.6)
	3	7 (5.3)
	4	8 (6.1)
	5	1 (0.8)
	6	0 (0)
Syndromes	AESD	36 (27.5)
	MERS	17 (13.0)
	ANE	2 (1.5)
	HSES	10 (7.6)
	FIRES/AERRPS	6 (4.6)
	ABS/Reye like	3 (2.3)
	Unclassified	57 (43.5)
Virus	FluA	15 (11.5)
	SARS-CoV2	19 (14.5)
	RSV	10 (7.6)
	HHV6/7	7 (5.3)
	Adeno virus	5 (3.8)
	hMPV	5 (3.8)
	Rota virus	1 (0.8)
	HSV	1 (0.8)
Treatment	TTM	64 (48.9)
	High dose corticosteroid	72 (55.0)
	Vitamins	75 (57.3)
	Immunoglobulin therapy	16 (12.2)
Post PCPC	1	63 (48.1)
	2	14 (10.6)
	3	21 (16.0)
	4	15 (11.5)
	5	3 (2.3)
	6	15 (11.5)
ΔPCPC	0	79 (60.3)
	1	16 (12.2)
	2	13 (9.9)
	3	9 (6.9)
	4	3 (2.3)
	5	11 (8.4)

Data are presented as the median (interquartile range).
PCPC, the Pediatric Cerebral Performance Category; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; MERS, clinically mild encephalitis/encephalopathy with a reversible splenial lesion; ANE, acute necrotizing encephalopathy; HSES, hemorrhagic shock and encephalopathy; FIRES, Febrile infection related epilepsy syndrome; AERRPS, acute encephalitis with refractory, repetitive partial seizures; ABS, acute brain swelling; FluA, influenza virus type A; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; RSV, respiratory syncytial virus; HHV6/7, human herpesvirus 6/7; hMPV, human metapneumovirus; HSV, herpes simplex virus; TTM, targeted temperature management.

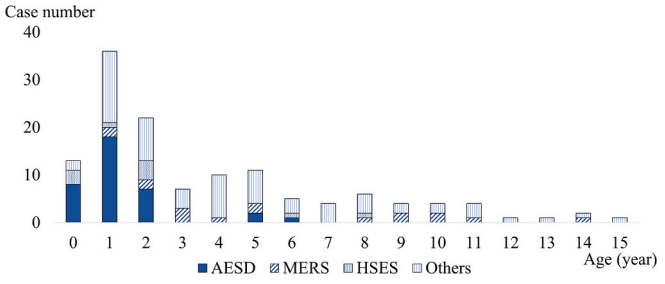

Fig. 1. Age distribution of acute encephalopathy.
AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; MERS, clinically mild encephalitis/encephalopathy with a reversible splenial lesion;
HSES, hemorrhagic shock and encephalopathy.

(HSES) (10 cases, 7.6 %). SARS-CoV-2 was the most common pathogen (19 cases, 14.5 %), followed by influenza virus type A (FluA) (15 cases, 11.5 %), and respiratory syncytial virus (RSV) (10 cases, 7.6 %). FluA was most common from January to March 2020, but there were no cases between April 2020 and December 2022. SARS-CoV-2 was most commonly detected from April to December 2022 (Fig. 2). Overall, TTM, high-dose corticosteroid therapy, and vitamin therapy were applied to approximately half of the cases; however, immunoglobulin therapy was performed for only 16 cases (12.2 %). Sequelae were observed in 52 (39.7 %) patients.

3.2. Comparison of characteristics of the patients by acute encephalopathy syndrome

The details of the three most common syndromes are presented in Table 2. The age of onset was significantly higher for the MERS group than for the other major syndrome groups (64 months, $P < 0.01$). FluA infections were significantly more frequent in patients with MERS than in those with AESD. There were no significant differences between the frequency of detections of SARS-CoV-2 among the major syndromes. The prevalence of sequelae differed across the following groups: MERS, 1/17 (5.9 %); AESD, 18/36 (50.0 %); and HSES, 9/10 (91.7 %). There were no deaths in the AESD group and 6/10 (60.0 %) deaths in the HSES group.

3.3. Comparison of treatment and management by acute encephalopathy syndrome

The treatments for the three most common syndromes are presented in Table 3. TTM was performed for 25 (69.4 %) of 36 patients with AESD; 5 (50.0 %) of 10 patients with HSES; and only 1 (5.9 %) of 17 patients with MERS ($p < 0.01$). High-dose corticosteroids were administered to 9 (90.0 %) of 10 patients with HSES and 11 (30.6 %) of 36 patients with AESD ($p < 0.01$). Vitamins were administered to 26 (72.2 %) of 36 patients with AESD and 9 (90.0 %) of 10 patients with HSES. Cyclosporine and blood purification therapies were not performed for any of the syndromes. Continuous EEG monitoring was conducted for 28 (77.8 %) of 36 patients with AESD; 6 (60.0 %) of 10 patients with HSES; and 2 (11.8 %) of 17 patients with MERS ($p < 0.01$).

4. Discussion

This was the first multicenter study to identify the epidemiology, treatment, and management of acute encephalopathy in a prospective consecutive case series. We considered the age of onset, pathogen, syndrome, and treatment in comparison to previous studies [3–5,10,11].

The most common age of onset of acute encephalopathy was 1 year, with most cases occurring during infancy. This is consistent with previous reports [4]. The median ages of onset for the syndromes were as follows: AESD, 17 months; HSES, 26 months; and MERS, 64 months. These are also comparable to those reported by previous studies [3]. MERS occurs at an older age than the other major syndromes.

The causative pathogen for acute encephalopathy was predominantly SARS-CoV-2, although FluA was comparatively prevalent. During our survey period, the prevalent SARS-CoV-2 strains were as follows: the ancestral strain was dominant until February 2021; the Alpha variant was dominant from March 2021 to June 2021; the Delta variant was dominant from July 2021 to December 2021; and the Omicron variant was dominant from January 2022 to August 2023 [6,12]. The proportion of cases of acute encephalopathy caused by the influenza virus was 27.3 % in 2010 and 17.4 % in 2017, both of which were the highest proportions in previous reports [4]. The proportion in this study differed. During the COVID-19 pandemic, the incidence of influenza virus-related acute encephalopathy decreased from 2020 to 2022. In contrast, SARS-CoV-2-related encephalopathy increased from January 2022, the period coinciding with the SARS-CoV-2 outbreak in children in Japan [6]. Influenza virus and SARS-CoV-2 infections have coexisted

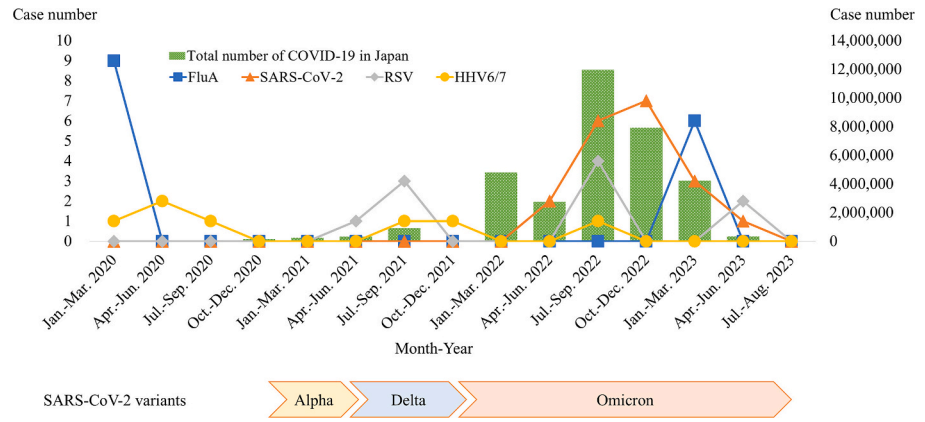

Fig. 2. Temporal distribution of the causative pathogen for acute encephalopathy.
COVID-19, Coronavirus disease 2019; FluA, influenza virus type A; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; RSV, respiratory syncytial virus; HHV6/7, human herpesvirus 6/7.
The left axis represents the number of acute encephalopathy cases, whereas the right axis represents the number of COVID-19 cases.

in Japan since 2023. Our results indicated that the causative pathogens of acute encephalopathy are significantly influenced by viral epidemics. Therefore, the proportion of the causative pathogens may change further in the future.

AESD was the most common syndrome, followed by MERS, which is consistent with the findings of previous studies. However, in previous nationwide surveys, acute necrotizing encephalopathy (ANE) was the third most common, instead of the HSES observed in this study [4]. The most common pathogen associated with ANE is the influenza virus [3,13]. In this study, one of two cases of ANE was positive for FluA. The decrease in influenza virus infections during the SARS-CoV-2 pandemic period may have contributed to the low number of ANE cases. The high prevalence of HSES may be attributed to the higher prevalence of HSES in patients with SARS-CoV-2-related encephalopathy [10,11]. Of the 10 patients with HSES in our study, three tested positive for SARS-CoV-2. Furthermore, the participation of multiple tertiary care centers in this study may have increased the proportion of HSES cases due to the transfer of severely ill patients.

This study aimed to investigate the treatment and management of acute encephalopathy. Specifically, we clarified the treatment options for each acute encephalopathy syndrome. Several important observations were made on comparing the outcomes of this study with those of the 2021 survey [5]. TTM, a specific treatment for acute encephalopathy, was performed for approximately half of all cases of acute encephalopathy in this study, and in 70 % of the AESD cases. A 2021 survey reported that 51 % of institutions preferred TTM for treating AESD, which was significantly higher than what was reported in 2015 [5]. TTM is the main treatment option for AESD. This may be influenced by reports indicating that TTM performed within 24 h of onset can improve outcomes for patients with a high risk of progression to acute encephalopathy, such as refractory convulsive status epilepticus [14,15].

In the 2021 survey study, high-dose corticosteroid therapy was administered to 85 % of AESD cases [5]. In this study, it was only administered to approximately 30 % of the cases. The ineffectiveness of high-dose corticosteroid therapy for AESD may have influenced this result [16]. In contrast, high-dose corticosteroid therapy was administered at a higher rate in the HSES group, which is consistent with previous reports [5]. No reports have demonstrated the effectiveness of high-dose corticosteroid therapy for HSES, but early high-dose corticosteroid therapy has been reported to improve the outcomes of ANE [17]. High-dose corticosteroid therapy may have been chosen for HSES cases, given that HSES is a type of cytokine storm-associated acute encephalopathy that is comparable to ANE.

Vitamin therapy was the treatment of choice for acute encephalopathy to improve mitochondrial dysfunction. A 2021 survey reported an increase in institutions choosing vitamin therapy for each acute encephalopathy syndrome compared with that in 2015 [5]. In this study, vitamins were administered to approximately half of the cases of encephalopathy, at rates of 70 % for AESD and 90 % for HSES. Vitamin therapy may have been selected frequently due to its reported benefits, such as prevention, improvement of prognosis [18], and minimal side effects [19].

A 2021 survey reported increasing adoption of continuous EEG monitoring for various acute encephalopathy syndromes by institutions [5]. In this study, continuous EEG monitoring was performed for approximately 78 % of the AESD cases and 60 % of HSES cases. Several studies have reported that continuous EEG monitoring identifies electrographic seizures in approximately 30–40 % of patients with critical illness [20–26]. It has also been reported that electrographic seizures are associated with mortality and poor neurological outcomes [24–27]. Therefore, continuous EEG monitoring in patients with acute encephalopathy is important for detecting electrographic seizures and providing appropriate treatment. However, continuous EEG monitoring requires equipment and staff with EEG-decoding skills, which makes it unavailable in all institutions. In this study, the high rate of continuous EEG monitoring may be attributed to the inclusion of multiple tertiary care centers.

In a study conducted in 2021, high-dose corticosteroids were administered to approximately half of the MERS cases [5]. However, they were administered to only a few cases of MERS in this study, and other treatments were infrequent. The prognosis of MERS is generally good [28], as evidenced in this study, despite the absence of specific treatment for most MERS cases.

However, this study did not aim to identify the most effective treatment. Further case enrollment and additional analyses are required to investigate the factors that may reduce the sequelae of acute encephalopathy or prevent its progression.

This study had several limitations. First, it involved fewer cases than other national surveys. However, the number of registered cases increased with time. We anticipate that the accumulation of more cases will allow us to analyze the treatments, their effectiveness, and the outcomes for each syndrome. Second, there may have been selection bias due to the predominance of tertiary care centers participating in this registry study and consequent higher proportion of severe cases.

In conclusion, we elucidated the epidemiology, treatment, and management of acute encephalopathy through a prospective multicenter consecutive case registry. The primary causative pathogen of acute encephalopathy, which was the influenza virus until the SARS-CoV-2 outbreak, changed to SARS-CoV-2 during the study. Compared

Table 2
Comparison of characteristics of the patients by acute encephalopathy syndrome.

Syndromes		AESD, N (%)	MERS, N (%)	HSES, N (%)	*P* value
Number		36	17	10	
Sex, male		17 (47.2)	7 (41.2)	7 (70.0)	0.33
Age, months [IQR]		17 [12, 24]	64 [37, 111]	26 [10.5, 34.5]	< 0.01*
Pre PCPC	1	29 (80.6)	17 (100.0)	9 (90.0)	0.67
	2	3 (8.3)	0 (0)	0 (0)	
	3	3 (8.3)	0 (0)	1 (10.0)	
	4	1 (2.8)	0 (0)	0 (0)	
	5	0 (0)	0 (0)	0 (0)	
	6	0 (0)	0 (0)	0 (0)	
Virus	FluA	2 (5.6)	5 (29.4)	1 (10.0)	0.04†
	SARS-CoV2	4 (11.1)	1 (5.9)	3 (30.0)	0.20
	RSV	2 (5.6)	1 (5.9)	1 (10.0)	0.80
	HHV6/7	5 (13.9)	0 (0)	0 (0)	0.21
	Adeno virus	0 (0)	1 (5.9)	0 (0)	0.43
	hMPV	2 (5.6)	0 (0)	0 (0)	1.0
	Rota virus	0 (0)	1 (5.9)	0 (0)	0.43
	HSV	0 (0)	0 (0)	0 (0)	
Post PCPC	1	13 (36.1)	16 (94.1)	1 (10.0)	< 0.01‡
	2	8 (22.2)	0 (0)	0 (0)	
	3	11 (30.6)	1 (5.9)	1 (10.0)	
	4	4 (11.1)	0 (0)	2 (20.0)	
	5	0 (0)	0 (0)	0 (0)	
	6	0 (0)	0 (0)	6 (60.0)	
ΔPCPC	0	18 (50.0)	16 (94.1)	1 (10.0)	< 0.01§
	1	9 (25.0)	0 (0)	1 (10.0)	
	2	6 (16.7)	1 (5.9)	1 (10.0)	
	3	3 (8.3)	0 (0)	1 (10.0)	
	4	0 (0)	0 (0)	0 (0)	
	5	0 (0)	0 (0)	6 (60.0)	

Data are presented as the median (interquartile range).
PCPC, Pediatric Cerebral Performance Category; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; MERS, clinically mild encephalitis/encephalopathy with a reversible splenial lesion; HSES, hemorrhagic shock and encephalopathy; FluA, influenza virus type A; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; RSV, respiratory syncytial virus; HHV6/7, human herpes virus 6/7; hMPV, human metapneumovirus; HSV, herpes simplex virus.
*AESD vs. MERS, P < 0.001; MERS vs. HSES, *P* < 0.05.
†AESD vs MERS, P < 0.05.
‡AESD vs MERS, P < 0.001; AESD vs HSES, P < 0.001; MERS vs HSES, *P* < 0.001.
§AESD vs MERS, P < 0.05; AESD vs HSES, *P* < 0.001; MERS vs HSES, P < 0.001.

with a previous report, TTM was performed more frequently for AESD, whereas high-dose corticosteroid therapy was less commonly used. Specific treatments for MERS were rarely administered. We determined the treatment choices for each acute encephalopathy syndrome. Further studies are required to evaluate the efficacies of these treatments.

Funding

This work was partly supported by JSPS KAKENHI [grant number JP22K09119 and 23K15630] to MN and ST, and a Grant-in-Aid for Research on Measures for Intractable Diseases [grant number 24FC1010] from the Ministry of Health, Labour, and Welfare to HN.

Author contributions

ST designed the project, participated in the data analysis and first drafted the manuscript. MN and HN designed and supervised the project and critically reviewed and revised the manuscript for important intellectual content. HY, KS, MM, MK, YH, AM, DT, TN, and GK collected data, and revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

CRediT authorship contribution statement

Shoichi Tokumoto: Writing – original draft, Visualization, Investigation, Funding acquisition, Data curation, Conceptualization. **Masahiro Nishiyama:** Writing – review & editing, Supervision, Project administration, Investigation. **Hiroshi Yamaguchi:** Writing – review & editing, Investigation. **Kentaro Sano:** Writing – review & editing, Investigation. **Mitsuo Motobayashi:** Writing – review & editing, Investigation. **Mitsuru Kashiwagi:** Writing – review & editing, Investigation. **Yuka Hattori:** Writing – review & editing, Investigation. **Azusa Maruyama:** Writing – review & editing, Investigation. **Daisaku Toyoshima:** Writing – review & editing, Investigation. **Taku Nakagawa:** Writing – review & editing, Investigation. **Go Kawano:** Writing –

Table 3
Comparison of treatments and management for acute encephalopathy syndrome.

Syndromes	AESD, N (%)	MERS, N (%)	HSES, N (%)	P value
Treatment				
TTM	25 (69.4)	1 (5.9)	5 (50.0)	< 0.01‖
High dose corticosteroid	11 (30.6)	2 (11.8)	9 (90.0)	< 0.01¶
Vitamins	26 (72.2)	2 (11.8)	9 (90.0)	< 0.01‡
Immunoglobulin therapy	2 (5.6)	1 (5.9)	3 (30.0)	0.08
Free radical scavengers	14 (38.9)	2 (11.8)	4 (40.0)	0.11
Osmo-therapy	6 (16.7)	1 (5.9)	4 (40.0)	0.09
Continuous EEG monitoring	28 (77.8)	2 (11.8)	6 (60.0)	< 0.01††

TTM: targeted temperature management.
EEG and electroencephalography.
‖AESD vs MERS, P < 0.001.
¶AESD vs HSES, P < 0.01; MERS vs HSES, *P* < 0.001.
‡AESD vs. MERS, *P* < 0.001; MERS vs. HSES, *P* < 0.001.
††AESD vs MERS, P < 0.001; MERS vs HSES, P < 0.05.

review & editing, Investigation. **Hiroaki Nagase:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgments

We would like to express our great appreciation to all the physicians who participated in this study. We also thank the Clinical and Translational Research Center of Kobe University for their statistical analysis support. We would also like to thank Editage (www.editage.com) for the English language editing.

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