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Clinical characteristics of SARS-CoV-2-associated encephalopathy in children: Nationwide epidemiological study

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ABSTRACT

Objective: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) sometimes triggers acute encephalopathy as a serious neurological complication in children. We previously reported the clinico-radiological findings of SARS-CoV-2-associated encephalopathy. The advent of the SARS-CoV-2 omicron variant led to a marked increase in pediatric patients with coronavirus disease 2019 (COVID-19); however, epidemiological changes with acute encephalopathy according to the emergence of SARS-CoV-2 have not yet been documented. Therefore, the present study investigated epidemiological differences in SARS-CoV-2-associated encephalopathy during the BA.1/BA.2 and BA.5 predominant periods and also between SARS-CoV-2-associated and non-SARS-CoV-2-associated encephalopathy.

Methods: We conducted a nationwide survey of SARS-CoV-2-associated encephalopathy in Japanese children between June and November 2022. We compared the present results during the BA.5 predominant period and previous findings during the BA.1/BA.2 predominant period. We also compared the clinico-radiological syndromes of encephalopathy between SARS-CoV-2-associated and non-SARS-CoV-2-associated encephalopathy.

Results: Although many patients with SARS-CoV-2-associated encephalopathy in the BA.5 predominant period had seizures as their initial symptoms, no significant differences were observed in the clinical features. Patients with SARS-CoV-2-associated encephalopathy had worse outcomes than those with non-SARS-CoV-2-associated encephalopathy (p-value = 0.003). Among 103 patients with SARS-CoV-2-associated encephalopathy, 14 (13.6%) had severe types of acute encephalopathy, namely, encephalopathy with acute fulminant cerebral

Abbreviations: AESD, Acute encephalopathy with biphasic seizures and late reduced diffusion; AFCE, Encephalopathy with acute fulminant cerebral edema; ANE, Acute necrotizing encephalopathy; COVID-19, Coronavirus disease 2019; FIRES, Febrile infection-related epilepsy syndrome; HSES, Hemorrhagic shock and encephalopathy syndrome; MERS, Clinically mild encephalitis/encephalopathy with a reversible splenial lesion; MIS-C, Multisystem inflammatory syndrome in children; PCPC score, Pediatric cerebral performance category score; PIMS-TS, Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

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edema (AFCE) and hemorrhagic shock and encephalopathy syndrome (HSES). Also, 28 (27.2%) patients with SARS-CoV-2-associated encephalopathy had poor outcome: severe neurological sequelae or death. Ninety-five patients (92.2%) were not vaccinated against SARS-CoV-2.
Conclusions: In SARS-CoV-2-associated encephalopathy, high percentages of AFCE and HSES can result in poor outcomes.

1. Introduction

A pandemic of omicron subvariants in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection led to a marked increase in the number of pediatric patients with coronavirus disease 2019 (COVID-19). Neurological complications related to COVID-19 also increased during the omicron epidemic; however, the overall outcomes of COVID-19 in children were favorable [1–3]. Among neurological disorders, acute encephalopathy is a common brain complication of SARS-CoV-2 infection [1,4]. Acute encephalopathy is characterized by the acute onset of disturbance of consciousness and/or an altered mental status, and is often preceded by febrile illness due to common viral infections [5]. Such infection-triggered encephalopathy syndromes are most common in infancy and childhood and often leave neurological sequelae [6,7].

We previously reported the findings of a nationwide survey on SARS-CoV-2-associated encephalopathy in Japanese children. We revealed that an increase in pediatric patients with COVID-19 resulted in a high incidence of SARS-CoV-2-associated encephalopathy, and some cases developed severe neurological symptoms and died [8].

The evolution of the omicron BA.1/BA.2 subvariants to the BA.5 subvariant occurred in Japan in 2022. With the appearance of the omicron variant in Japan, the number of pediatric patients requiring hospitalization increased from that in the pre-omicron epidemic period [3]. However, it remains unclear whether the number of cases of SARS-CoV-2-associated encephalopathy increased or if its clinical features were affected by shifts in the subvariants.

We performed a nationwide survey on the neurological complications of COVID-19 in Japanese children between June 1 and November 30, 2022. We compared the present results during the BA.5 predominant period and previous findings during the BA.1/BA.2 predominant period to identify any differences. We also compared SARS-CoV-2-associated and non-SARS-CoV-2-associated encephalopathy to obtain more detailed information on the clinical characteristics and outcomes of COVID-19.

2. Materials and methods

2.1. Subjects

The present study included Japanese children younger than 18 years who developed acute encephalopathy preceded by or concurrent to SARS-CoV-2 infection with an onset between June 2022 and November 2022. In Japan, the omicron BA.5 subvariant was prevalent during the period of this survey. Our previous survey was performed between January 2020 and May 2022 and, thus, involved periods when the ancestral strain and several SARS-CoV-2 variants of concerns were dominant [9]. The methods and diagnostic criteria used were essentially the same between both surveys [8]. We defined SARS-CoV-2-associated encephalopathy as meeting all of the following criteria: 1) an acute onset of impaired consciousness (Glasgow Coma Scale <11 or Japan Coma Scale >20) or disturbance of consciousness, such as abnormal behavior or a personality change that lasts for 24 h or longer (Supplementary Table 1) [10]; 2) an acute onset of neurological symptoms within 2 weeks of the diagnosis of COVID-19 or COVID-19-associated multisystem inflammatory syndrome in children (MIS-C)/pediatric Inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) [11,12]; 3) proof of infection with SARS-CoV-2 (PCR method, antigen test, antibody test, and other specimen tests); 4) the exclusion of other diseases, such as cerebrovascular disorders, meningitis, acquired demyelinating syndromes, acute disseminated encephalomyelitis, autoimmune encephalitis, and posterior reversible encephalopathy syndrome. Patients with underlying diseases were included in the analysis. Informed consent was waived because this was an epidemiological survey. The present study was approved by the Institutional Review Board of Tokyo Metropolitan Institute of Medical Science (#20–28).

2.2. Web-based survey and clinico-radiological syndromes

We conducted a web-based survey among pediatricians affiliated with the Japanese Society of Child Neurology between December 14, 2022 and January 15, 2023. If more than one society member belonged to a facility, one of them answered on behalf of the facility. The members also included with rehabilitation physicians or general practitioners who were not involved in acute care. Questionnaire items included age of onset, sex, a clinical diagnosis of acute encephalopathy syndrome, a history of COVID-19 vaccination, the presence of underlying diseases, neurological symptoms at onset, and complications by MIS-C/PIMS-TS, and outcomes. We then investigated whether patients were categorized into six syndromes according to their clinico-radiological manifestations: acute encephalopathy with biphasic seizures and late reduced diffusion (AESD); encephalopathy with acute fulminant cerebral edema (AFCE); acute necrotizing encephalopathy (ANE); febrile infection-related epilepsy syndrome (FIRES); hemorrhagic shock and encephalopathy syndrome (HSES); and clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS), as shown in Supplementary Table 2 [10,13,14]. AFCE is one of the severe types of encephalopathy resulting in high mortality, recently recognized. AFCE is defined as follows: fever, altered mental status, and/or new-onset seizures with progressive diffuse cerebral edema. To diagnose AFCE, we have to exclude cases with organic brain injury or metabolic disorder, marked hyponatremia, or pre-existing neurological diseases [14]. Since FIRES is classified as an acute encephalopathy in Japan, we included FIRES in the present survey as a SARS-CoV-2-associated syndrome. Outcomes were evaluated using pediatric cerebral performance category (PCPC) scores at hospital discharge [15].

2.3. Study period

We compared cases with an onset during the BA.5 predominant period between June 1, 2022 and November 30, 2022 and those with an onset during the BA.1/BA.2 predominant period between January 1, 2022 and May 31, 2022. The BA.1/BA.2 subvariants were epidemic during the previous survey period in Japan and were replaced by BA.5 around June 2022, with BA.5 accounting for 90% of the subvariants detected in Japan by late July 2022 [16]. We also examined differences in clinico-radiological syndromes between SARS-CoV-2-associated and non-SARS-CoV-2-associated encephalopathy. Regarding comparisons with non-SARS-CoV-2 encephalopathy, SARS-CoV-2-associated encephalopathy that developed prior to January 2022 was also included and data from both surveys were combined to involve the periods of the ancestral strain and the alpha through delta predominance. Clinical information on cases in the combined SARS-CoV-2 group was compared with that on non-SARS-CoV-2-associated encephalopathy with an onset between March 2014 and October 2017 based on a previous study [7].

2.4. Statistical analysis

We performed statistical analyses using the Mann-Whitney *U* test to compare discrete variables and the chi-squared test or Fisher's exact test to compare categorical variables. The significance of differences was set at $p < 0.05$. Bonferroni correction was applied for multiple comparisons. Statistical analyses were performed using R software, version 3.6.2 (R Project for Statistical Computing).

3. Results

3.1. Response rate and number of subjects

Among the 3802 members of the Japanese Society of Child Neurology, 144 responded. The response rate was low at 3.8%, but was similar to that in the previous survey (Table 1). The total number of patients with neurological manifestations associated with SARS-CoV-2 infection was 79 in the present survey. Eleven of these cases were excluded because 10 did not meet the criteria for acute encephalopathy and 1 was a duplicate case (Fig. 1). We collected 68 cases of SARS-CoV-2-associated encephalopathy that met the criteria for analysis in the present survey when BA.5 was predominant. Additionally, eligible patients from the previous survey period were reviewed to compare data between both surveys. Thirty-two patients with SARS-CoV-2-associated encephalopathy met the criteria between January 1, 2022 and May 31, 2022 in the previous survey during the BA.1/BA.2 predominant period (Fig. 1).

3.2. Comparison of encephalopathy between BA.1/BA.2 and BA.5 predominant periods

We compared the clinical characteristics and prognosis of SARS-CoV-2-associated encephalopathy between the previous and current surveys (Tables 1, 2). In the previous survey between January and May 2022, approximately 1.98 million patients aged <20 years had COVID-19, while in the present study between June and November 2022, approximately 3.97 million patients were recorded. The ratio of the number of patients with SARS-CoV-2-associated encephalopathy to the total number of COVID-19 patients of the same generation was similar between the two studies (Table 1). No significant difference was observed in the incidence of encephalopathy between the BA.1/BA.2 and BA.5 predominant periods.

Ages at the onset of encephalopathy ranged between 0 and 15 years (median = 3 years) and the male to female ratio was 1.6:1 in the present survey (Table 2). Similar to the previous survey, the majority of SARS-CoV-2-associated encephalopathy patients had not been vaccinated (among 68 patients, 61, 3 and 4 were unvaccinated, vaccinated, and unknown, respectively). Underlying diseases affecting neurodevelopment accounted for 27.9% of cases of SARS-CoV-2-associated encephalopathy in the BA.5 predominant period. The first symptoms of SARS-CoV-2-associated encephalopathy were seizures, impaired consciousness, and abnormal speech and behavior, which accounted for >90% of cases. The prognosis of patients did not significantly differ between the two groups. In the present study, 25 patients (36.8%) recovered to their baseline state (PCPC = 1), while 34 (50.0%) had neurological disability (PCPC = 2–5) and 7 (10.3%) died (PCPC = 6).

3.3. SARS-CoV-2-associated and non- SARS-CoV-2-associated encephalopathy

To compare the clinical features and outcomes of non-SARS-CoV-2-associated encephalopathy with those of SARS-CoV-2-associated encephalopathy, we re-examined the clinico-radiological syndromes and outcomes of non-SARS-CoV-2-associated encephalopathy using the findings of our previous national epidemiological survey of acute encephalopathy in 2014–2017. A total of 1211 patients with non-SARS-CoV-2-associated encephalopathy met the criteria between March 2014 and October 2017. In the combined study on SARS-CoV-2-associated encephalopathy (between January 2020 and November 2022), we added 3 patients who developed SARS-CoV-2-associated encephalopathy between January 2020 and December 2021. Therefore, 103 patients met the criteria in the combined study (Fig. 2).

Among the six clinico-radiological syndromes examined (AESD, AFCE, ANE, FIRES, HSES, and MERS), AESD was the most common (Fig. 3). The percentages of AFCE and HSES, severe syndromes commonly causing neurological disability or death, were higher in SARS-CoV-2-associated encephalopathy than in non-SARS-CoV-2-associated encephalopathy. The percentage of MERS, a mild and the second most common syndrome, was low. Age at onset was significantly older for SARS-CoV-2-associated encephalopathy than for non-SARS-CoV-2-associated encephalopathy (*p*-value = 0.00001) (Fig. 4).

The outcomes of SARS-CoV-2-associated encephalopathy differed from those of non-SARS-CoV-2-associated encephalopathy. Recovery to the pre-symptomatic state (PCPC = 1) was observed in 45 patients (43.7%), mild to moderate neurological sequelae (PCPC = 2–3) in 28 (27.2%), severe neurological sequelae (PCPC = 4–5) in 17 (16.5%), and death in 11 (10.7%) (Table 3). SARS-CoV-2-associated encephalopathy was detected in significantly more patients with severe disability or death than non-SARS-CoV-2-associated encephalopathy (*p*-value = 0.003).

3.4. Impact of underlying disorders on encephalopathy types

No significant differences were noted in acute encephalopathy syndromes between patients with and without underlying diseases affecting neurodevelopment (Supplementary Table 3).

3.5. Vaccination against SARS-CoV-2

Among 103 patients with SARS-CoV-2-associated encephalopathy, 95 (92.2%) had not been vaccinated against SARS-CoV-2 (4 each vaccinated and unknown). All patients with AFCE and HSES were unvaccinated against SARS-CoV-2.

4. Discussion

The present study is the largest nationwide survey of the clinical characteristics of SARS-CoV-2-associated encephalopathy (103 cases)

Table 1
Basic information from previous and present surveys.

Survey	Previous survey	Present survey
Surveyed period	January 2022–May 2022	June 2022–November 2022
Dominant SARS-CoV-2 omicron subvariant	BA.1/BA.2	BA.5
Number of members of the Japanese Society of Child Neurology for the survey	3802	3802
Number of responses	217	144
Response rate	5.7%	3.8%
Number of patients with SARS-CoV-2-associated encephalopathy	32	68
Number of patients with COVID-19 in Japan (aged <20 years)	1,982,591	3,971,779

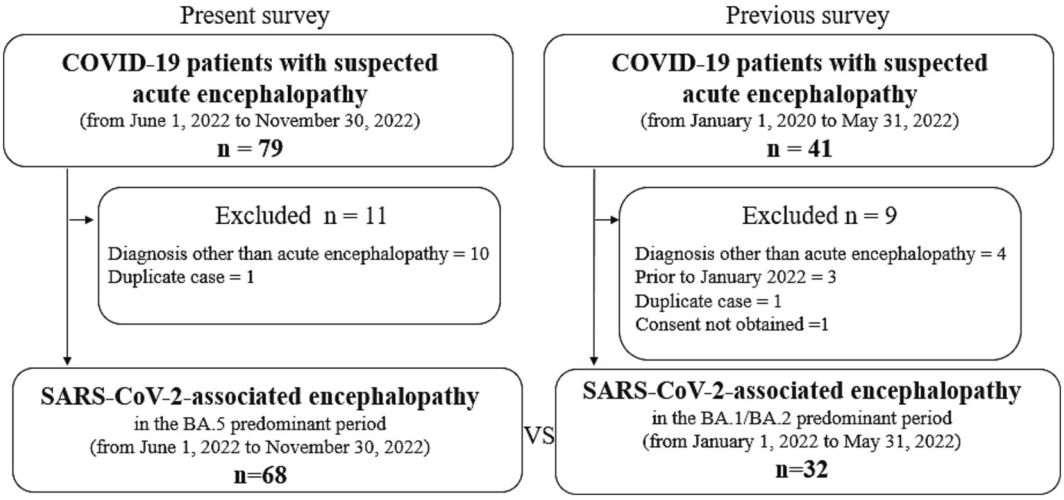

Fig. 1. Flowchart of subjects for SARS-CoV-2-associated encephalopathy during BA.5 and BA.1/BA.2 predominant periods.
Patients with underlying diseases were included in both periods.

Table 2
Clinical characteristics of SARS-CoV-2-associated encephalopathy between BA.1/BA.2 and BA.5 predominant periods.

	Previous survey (BA.1/BA.2 predominance) $n = 32$	Present survey (BA.5 predominance) $n = 68$	p-value
Age range (median)	0–14 years (5)	0–15 years (3)	0.08 *
Sex, male (%)	13 (40.6%)	42 (61.8%)	0.06
Vaccinated (%)	1 (3.1%)	3 (4.4%)	1
MIS-C (%)	5 (15.6%)	2 (2.9%)	0.04
Number of patients with underlying diseases affecting neurodevelopment (%)	5 (15.6%)	19 (27.9%)	0.2
Onset date of neurological symptoms (median)	0–8 (0)	0–8 (1)	0.2 *
Neurological symptoms at onset			
Seizure (%)	16 (50.0%)	50 (73.5%)	0.03
Decreased consciousness level (%)	8 (25.0%)	12 (17.6%)	0.4
Abnormal behavior (%)	7 (21.9%)	4 (5.9%)	0.03
Outcome (%)			0.4 *
PCPC = 1	18 (56.3%)	25 (36.8%)	
PCPC = 2	1(3.1%)	14 (20.6%)	
PCPC = 3	4 (12.5%)	9 (13.2%)	
PCPC = 4	4 (12.5%)	9 (13.2%)	
PCPC = 5	2 (6.3%)	2 (2.9%)	
PCPC = 6	3 (9.4%)	7 (10.3%)	

Examined using Fisher's exact test, except for *age, onset date, and outcome with the Mann–Whitney U test. Significance levels were adjusted by the number of comparisons to correct for multiple testing. The adjust significance threshold was set at $p < 0.005$ (adjusted $\alpha = 0.05/10$). Underlying diseases affecting neurodevelopment were included as follows: general developmental delay, autism spectrum disorder, complex febrile seizure, cerebral palsy, patients with very low birth weight, epilepsy, chromosome abnormality, genetic disorder, tuberous sclerosis complex, brain tumor, cavernous malformations, autoimmune disorder, and recurrent MERS. Outcomes were graded into a pre-symptomatic state (PCPC = 1), mild disability (PCPC = 2), moderate disability (PCPC = 3), severe disability (PCPC = 4), coma or vegetative state (PCPC = 5), and death (PCPC = 6).
Abbreviations: MIS-C, multisystem inflammatory syndrome in children; PCPC, pediatric cerebral performance category; MERS, clinically mild encephalitis/encephalopathy with a reversible splenial lesion.

during the SARS-CoV-2 omicron variant outbreak. Here, we reported the clinical features of SARS-CoV-2-associated encephalopathy in the BA.1/BA.2 and BA.5 predominant periods during the pandemic of omicron variants. Furthermore, we identified the clinical features of SARS-CoV-2-associated encephalopathy by classifying them into clinico-radiological syndromes. Few clinical differences and no change in the prognosis of SARS-CoV-2-associated encephalopathy was observed between the BA.1/BA.2 and BA.5 predominant periods. On the other hand, there was a 23.5% increase in the percentage of patients who developed seizures as the first neurological symptom in the BA.5 predominant period compared in the BA.1/BA.2 predominant period. A previous study reported that the hospitalization of Japanese children for febrile seizures was more frequent in the BA.5 predominant period than in the BA.1/BA.2 predominant period [17]. Therefore, the present results provide support for the higher risk of seizures with the BA.5 subvariant. In addition, more patients in the BA.1/BA.2 predominant period had abnormal behaviors as their first neurological symptoms than in the BA.5 predominant period. All the seven patients who presented abnormal behaviors in the BA.1/BA.2 predominant period achieved full recovery; one case was MERS and 6 were unclassified encephalopathy. The cases of unclassified encephalopathy with abnormal behaviors could have been MERS because the typical symptoms of MERS were abnormal behaviors and its prognosis are favorable.

The present study revealed that seizures, impaired consciousness, and abnormal speech and behavior accounted for >90% of the first symptoms of encephalopathy in the BA.1/BA.2 and BA.5 predominant periods. COVID-19 in children rarely shows severe respiratory symptoms [3,18]; however, neurological symptoms, such as seizures,

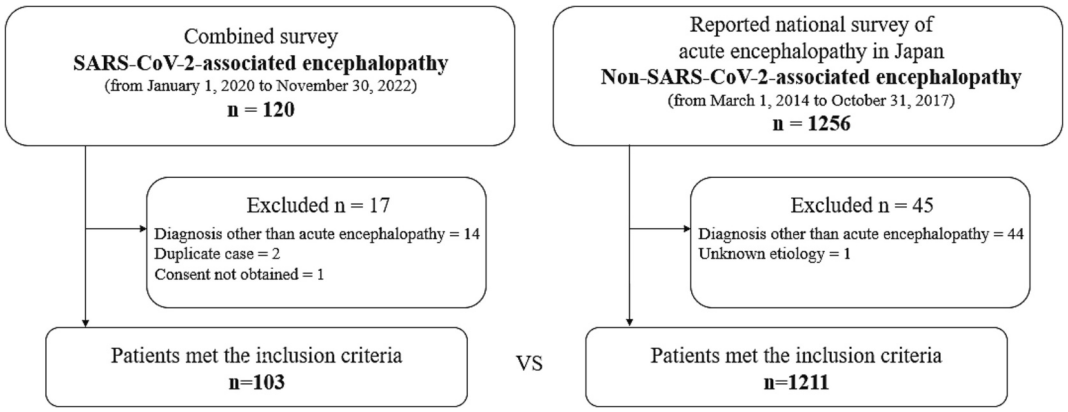

Fig. 2. Flowchart of subjects for SARS-CoV-2-associated and non-SARS-CoV-2-associated encephalopathy.
Patients with underlying diseases were included in the analysis. The combined survey involved the period when the ancestral SARS-CoV-2 strain and alpha through omicron variants predominated.

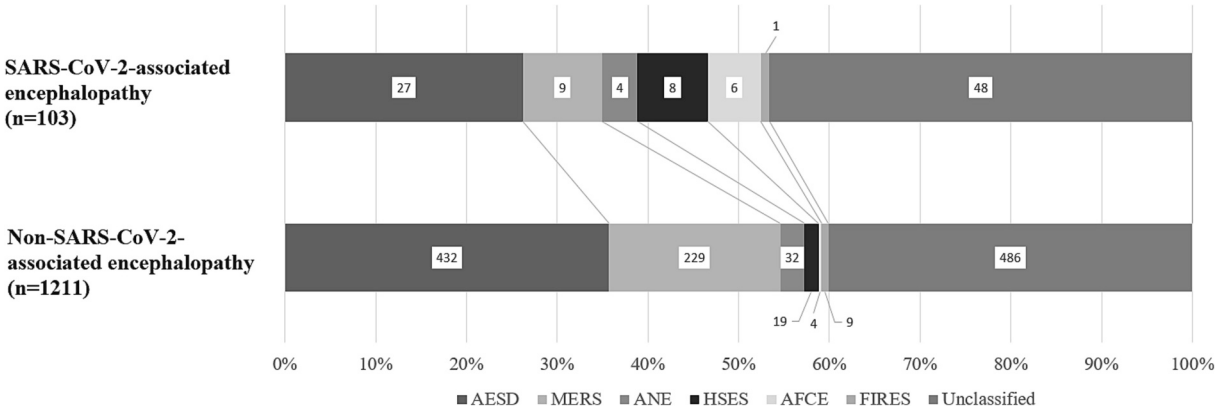

Fig. 3. Comparison of clinico-radiological encephalopathy syndromes between SARS-CoV-2-associated and non-encephalopathy SARS-CoV-2-associated encephalopathy.
The following conditions were excluded: cerebrovascular disorder, meningitis, acquired demyelinating syndromes, acute disseminated encephalomyelitis, autoimmune encephalitis, posterior reversible encephalopathy syndrome, hemolytic uremic syndrome, and metabolic encephalopathy.
Abbreviations: AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; AFCE, encephalopathy with acute fulminant cerebral edema; ANE, acute necrotizing encephalopathy; FIRES, febrile infection-related epilepsy syndrome; HSES, hemorrhagic shock and encephalopathy syndrome; MERS, clinically mild encephalitis/encephalopathy with a reversible splenial lesion.

impaired consciousness, and systemic symptoms, including vomiting and a poor oral intake, require caution because they may be the initial signs of encephalopathy.

We also compared clinical characteristics between SARS-CoV-2-associated encephalopathy and non-SARS-CoV-2-associated encephalopathy by classifying them into clinico-radiological syndromes. Some acute encephalopathy syndromes triggered by infection have a typical clinical course and specific neuroimaging findings [10,19]. The classification of acute encephalopathy into clinico-radiological syndromes enables us to predict the clinical course and presume the pathophysiology. Age at onset was older for SARS-CoV-2-associated encephalopathy than for non-SARS-CoV-2-associated encephalopathy. Previous studies reported that the number of children with febrile seizures due to COVID-19 increased during the recent omicron outbreak and also that the age at onset extended to older age groups [3,20,21], which appeared to be attributed to the majority of children being infected by SARS-CoV-2 for the first time and the age at SARS-CoV-2 infection being broad. The same reasons are plausible for the older ages at the onset of SARS-CoV-2-associated encephalopathy. Similarly, during the H1N1 influenza pandemic in 2009–2010, ages at the onset of influenza-associated acute encephalopathy in Japanese children were older than in the periods of seasonal influenza [7].

The present results revealed that the prognosis of patients with SARS-CoV-2-associated was worse than those with non-SARS-CoV-2-associated encephalopathy, with a larger number of cases resulting in severe neurological sequelae and death. The classification of clinico-radiological syndromes revealed that the percentages of AFCE and HSES, severe conditions causing severe neurological sequelae and death in many cases, were higher, whereas that of MERS, a mild syndrome leading to recovery in most cases, was lower in SARS-CoV-2-associated than in non-SARS-CoV-2-associated encephalopathy. One of the reasons for the higher percentages of severe syndromes may be the greater ability of SARS-CoV-2 to elicit severe responses of natural immunity in children. On the other hand, the lower number of MERS cases may be attributed to the difficulties associated with the MRI testing of COVID-19 patients because of quarantine after hospitalization. Therefore, transient lesions in the splenium of the corpus callosum, an indispensable finding for the diagnosis of MERS, may have been missed [22].

Several patients with AFCE related to COVID-19 were previously reported to be children. Pediatric cases of AFCE typically showed no previous medical history and severe progressions, often resulting in marked cerebral edema and multiple organ failure within hours of onset [8,23–25]. All six patients with SARS-CoV-2-associated AFCE during the omicron BA.2 outbreak in Taiwan initially had shock and five showed rapid progression to multiorgan failure [25]. Patients with HSES also presented with an acute onset of shock, convulsions and coma, bleeding,

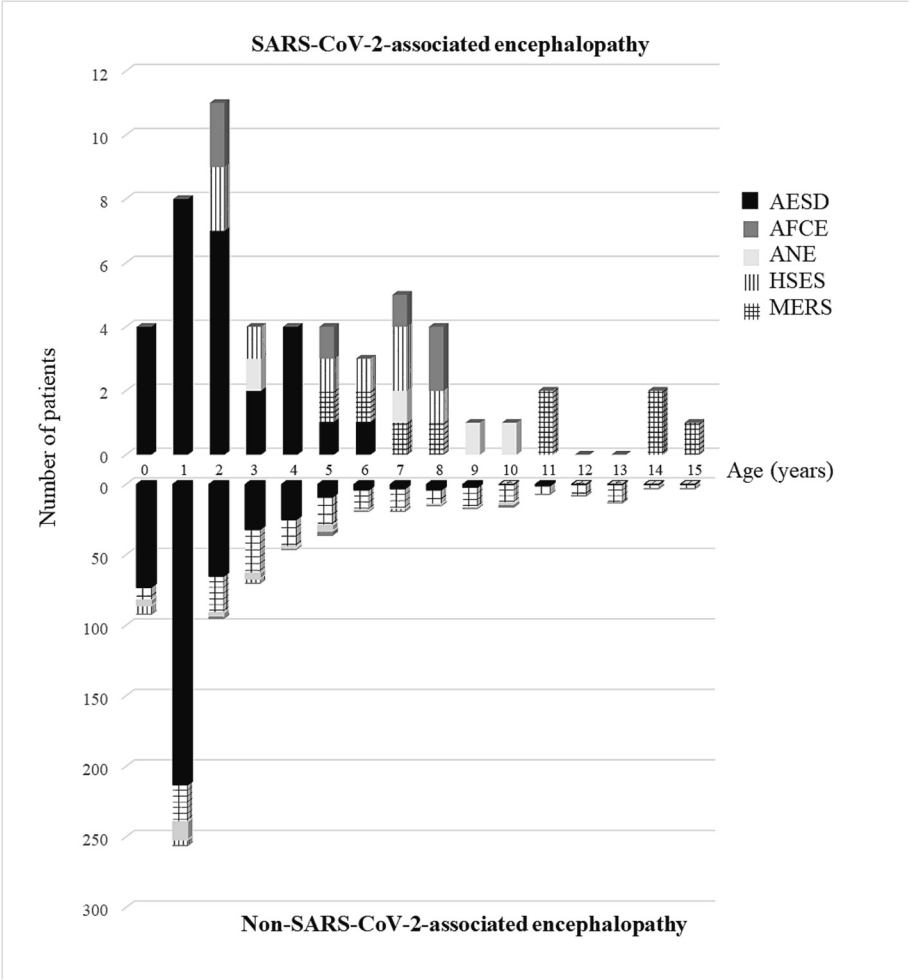

Fig. 4. Ages at the onset of SARS-CoV-2-associated and non-SARS-CoV-2-associated encephalopathy classified into clinico-radiological syndromes.
The median ages of each syndrome in SARS-CoV-2-associated encephalopathy were as follows: 2, 6, 9, 6, and 11 years for AESD, AFCE, ANE, HSES, and MERS, respectively. FIRES was not shown in the figure because there was only one patient.
Abbreviations: AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; AFCE, encephalopathy with acute fulminant cerebral edema; ANE, acute necrotizing encephalopathy; FIRES, febrile infection-related epilepsy syndrome; HSES, hemorrhagic shock and encephalopathy syndrome; MERS, clinically mild encephalitis/encephalopathy with a reversible splenial lesion.

Table 3
Neurological outcomes in patients with SARS-CoV-2-associated and non- SARS-CoV-2-associated encephalopathy.

	SARS-CoV-2-associated encephalopathy $n = 103$	Non-SARS-CoV-2-associated encephalopathy $n = 1211$	*p*-value
Outcome			0.003
Full recovery (%)	45 (43.7%)	684 (56.5%)	
Mild to moderate disability (%)	28 (27.2%)	288 (23.8%)	
Severe disability or vegetative state (%)	17 (16.5%)	142 (11.7%)	
Death (%)	11 (10.7%)	61 (5.0%)	
Unknown (%)	2 (1.9%)	36 (3.0%)	

Outcomes were graded as a full recovery or pre-symptomatic state (PCPC = 1), mild to moderate neurological disability (PCPC = 2–3), severe neurological disability or a vegetative state (PCPC = 4–5), and death. Data were examined using the Mann–Whitney *U* test.

elevated serum hepatic enzymes, acidosis, and impaired renal function [13,26]. The similar clinical manifestations of HSES and AFCE suggest that the two syndromes partially overlap. Since they are the most severe types of acute encephalopathy, HSES and AFCE may be the major causes of death related to COVID-19 in Japanese children. Difficulties are associated with diagnosing HSES and AFCE immediately after their onset, and, thus, useful diagnostic criteria and biomarkers for their diagnosis at onset are needed.

The present survey found no impact of underlying diseases on the percentage of acute encephalopathy syndromes (Supplementary Table 3), which disagrees with previous findings reporting the high susceptibility of children with certain underlying neurological disorders to AESD. Triggered by febrile infections, patients with tuberous sclerosis complex and other congenital disorders of cerebral cortical development are susceptible to AESD [27,28]. The reason for the absence of differences in the types of encephalopathy may be due to the small number of cases examined.

In the present survey, most of the patients with encephalopathy were not vaccinated against COVID-19. Furthermore, all the patients with HSES and AFCE were not vaccinated against SARS-CoV-2. Although previous studies demonstrated the usefulness of COVID-19 mRNA vaccines to prevent infection, symptomatic infection, and hospitalization [29,30], the preventive effects of the COVID-19 vaccine on the development of encephalopathy remain unknown. In the present study, we were unable to confirm vaccine effectiveness against SARS-CoV-2-associated encephalopathy because we did not examine data on

COVID-19 vaccination rates for Japanese children in the surveyed periods.

There are some limitations that need to be addressed. We could not precisely compare the results between the previous and current surveys because the response rates of them were low. This may have been due to facility representatives being asked to respond, and hospitals with pediatric departments often having no members of the Japanese Society of Child Neurology. However, the responses were obtained from 201 medical institutions in the previous survey and from 141 in the present survey. The number of facilities that replied in the two surveys was comparable to those that replied in the national epidemiological survey of acute encephalopathy in 2014–2017, suggesting the accuracy of the present results [7]. Another limitation is that AFCE was not defined in the national epidemiological survey of acute encephalopathy in 2014–2017, and we re-examined the original survey findings in the present study. Some cases of AFCE may have been overlooked in the previous study between 2014 and 2017. Moreover, detailed clinical information, laboratory data, and radiological findings were not obtained in the present survey. The BA.1, BA.2, and BA.5 subvariants in our cases were not identified by a phylogenetic analysis of SARS-CoV-2, they were decided by the onset periods when each subvariant predominated. Further studies are warranted to elucidate the clinical characteristics of severe cases.

5. Conclusion

The clinical presentation of SARS-CoV-2-associated encephalopathy during the BA5 predominant period was similar to that of BA.1/BA.2, while a high percentage of patients had seizures as the initial symptom. In comparisons with non-SARS-CoV-2-associated encephalopathy, cases of SARS-CoV-2-associated encephalopathy had worse outcomes with higher percentages of the severe encephalopathies, HSES and AFCE. The present results provide novel insights into the public health of pediatric infectious diseases and encephalopathy.

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Author's contributions

MK, HS, MM, and JT: concept and design. HS, YA, IK, YMa, KM, YM, HN, MN, AO, YS, HT, JT, and the Japanese Pediatric Neuro-COVID-19 Study Group: acquisition, analysis, and or interpretation of data. MK, HS, and JT: drafting of the manuscript. MK: statistical analysis. HS obtained funding, had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. AO and MM: supervision. All authors read and approved the submitted version.

Declaration of competing interest

The authors declare no competing interests.

Data availability

All data generated or analyzed during the present study are included in this published article and its supplementary information files. The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2024.122867.

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