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Original Article

Clinical features and virologic lineages of COVID-19-associated encephalitis in Taiwanese children during early epidemic wave of omicron in 2022: Report from a medical center

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Abstract *Background:* A surge of encephalitis was reported in children during the early wave of the omicron epidemic in Taiwan. Information on the COVID-19-associated encephalitis, including epidemiologic features and factors of unfavorable outcomes, remained unclear.
Methods: A total of 128 hospitalized Taiwanese children with laboratory-confirmed COVID-19 were enrolled between April 01, 2022, and May 31, 2022. The information on demographics and clinical features was abstracted from the medical records. Virologic lineages were determined by sequences of the spike protein. Factors associated with encephalitis and unfavorable outcomes were identified by comparisons to children without encephalitis and with favorable outcomes, respectively.
Results: The leading syndromes associated with COVID-19 in hospitalized children were febrile seizure (20, 15.7%), fever as the solitary symptom (18, 14.1%), and croup syndrome (14, 10.9%).

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Encephalitis was diagnosed in nine (7.03%) children. When compared to the three leading syndromes, children with encephalitis were at older ages, had greater rates of hypotension, PICU admissions, use of inotropic agents ($P < .001$ for all above comparisons), mortality ($P = .008$), and longer hospital stays ($P = .016$), but not the underlying comorbidities ($P = .376$). Unfavorable outcomes were identified in 3 (33.3%) of 9 encephalitis cases and associated with a lower Glasgow coma scale, hypotension, and higher C-reactive protein ($P < .05$ for all). BA.2.3.7 was the dominant sublineage in children with or without encephalitis.
Conclusions: Omicron BA.2.3.7 can cause fulminant and lethal encephalitis in healthy children. Depressed consciousness and hypotension at presentation were significant risks of unfavorable outcomes for pediatric COVID-19-associated encephalitis.

Introduction

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) was identified in more than 600 million cases globally, leading to at least 6.5 million deaths from the outbreak to October 2022.[1,2] Individuals of all age groups, including the pediatric population, were affected. As of May 2022, approximately 20% of laboratory-confirmed cases of COVID-19 were reported in children in the United States.[1,3] It has been well documented that the disease severity of COVID-19 was relatively mild in children compared to the adult population. Indeed, only an estimated 1.5% of children with SARS-CoV-2 infections required hospitalization in the early pandemic.[4] In a pooled data analysis from seven developed countries in the first year of the pandemic, the COVID-19-related death rate was 0.17 in 100,000 pediatric populations aged 0—19 years.[5] Severe COVID-19 usually occurs in children with underlying conditions including neuromuscular diseases, cardiovascular diseases, and pulmonary complex chronic condition.[6—8]

Neurologic events were among the most critical complications in COVID-19 patients. Most reports of neurologic complications of COVID-19 in adults have focused on vascular events, including cerebral infarction and ischemic stroke.[9,10] Among children, the range of diseases affecting the central nervous system seems distinct from those seen in adults, with most cases involving febrile seizures, nonfebrile seizures, and encephalopathy.[11—13] COVID-19-associated fulminant and fatal encephalitis was increasingly reported in children as the evolution of the pandemic.[14—16] Taiwan was well known for its excellent control of COVID-19, with an extremely low infection rate in the early phase of the pandemic.[17—19] Unfortunately, the first epidemic wave of the omicron variant in Taiwan, starting in April 2022, resulted in an increased number of pediatric cases. During the first two months of the omicron epidemic, acute encephalitis occurred unexpectedly in half of the children with severe or fatal COVID-19.[20,21] There have been incomplete reports on acute neurologic complications associated with COVID-19 in children.[14—16] To capture the picture of severe COVID-19 more comprehensively in children during the early omicron wave, we collected and analyzed the clinical features of all hospitalized children with laboratory-confirmed COVID-19 in a medical center, with a focus on the epidemiological characteristics, including the disease manifestations, treatment, and outcomes of children with neurologic complications.

Methods

Ethics statement

This study was approved by the Research and Ethics Committee of Chang Gung Memorial Hospital (IRB: 202201048B0). A waiver of consent was granted, given the retrospective nature of the project and the anonymous analysis of the clinical information of patients.

Study design

During April 01, 2022, and 31 May 2022, a list of in-patients aged equal to or younger than 18 years with a nasopharyngeal PCR positive for SARS-CoV-2 was retrieved from the clinical virology laboratory in Chang Gung Memorial Hospital, Linkou branch. The study period was designated to capture the early wave of the COVID-19 epidemic caused by the omicron variant in 2022 in Taiwan. The information on demographics, clinical features, and outcomes of COVID-19 was abstracted from the medical records by a standardized data collection form. Patients were excluded from the analysis if they were admitted for reasons other than COVID-19 and the SARS-CoV-2 was accidentally detected due to the routine screening policy of the hospital infection control. A selected set of PCR products with a Ct value less than 30 from the nasopharyngeal samples were sent for Sanger sequencing for subvariant lineage determination.

Case definitions

Encephalitis was defined according to the criteria proposed by the International Encephalitis Consortium in 2013 (10.1093/cid/cit458). Briefly, the major criteria and at least two minor criteria had to be fulfilled to diagnose "possible" encephalitis. An altered mental status with decreased or altered level of consciousness, lethargy, or personality change lasting $\geq$24 h without alternative cause was the required major criteria. The minor criteria included

(1). Body temperature ≥38 °C within three days of presentation, (2). Seizure activity, either in a generalized or partial form, is not fully attributable to known seizure disorders (3). New onset of focal neurologic symptoms/signs (4). Pleocytosis with a cerebrospinal fluid (CSF) white blood cell (WBC) count ≥5/μL (5). Neuroimage studies suggestive of encephalitis that was either new or appeared acute in onset (6). Electroencephalography (EEG) finding was consistent with encephalitis and not attributable to another cause. According to the Pediatric Advanced Life Support guidelines, hypotension was defined by the patient's age (7). Furthermore, severe encephalitis was defined as persistent hypotension after fluid resuscitation and receiving one vasopressor in an encephalitis patient.

Virologic study

RNA was extracted manually using the QIAamp Viral RNA Mini Kit (250) (Qiagen, Hilden, Germany). The whole genome sequencing was performed on the platform of Illumina and with the protocol of COVID-19seq Assay.[22] The genomes were assembled and searched for mutations on the region encoding Spike protein.

Statistical analysis

Statistical analysis was performed by Statistical Product and Service Solutions software version 24.0 (SPSS Inc., Chicago, IL, USA). For the continuous variables, the significance was determined using the independent t-test or Mann–Whitney U test where indicated. The categorical variables were analyzed by the chi-squared test or Fisher's exact test where appropriate. Multivariate logistic regression analysis was furtherly conducted to identify factors associated with encephalitis. The receiver operating characteristic curves was used to determine optimal cutoff values of the relevant parameters to predict severe encephalitis. $P < .05$ was considered statistical significance.

Results

Clinical features of pediatric COVID-19 in different age groups (Table 1)

A total of 139 children with laboratory-confirmed COVID-19 with PCR method admitted to a hospital were identified from April 1 to May 31, 2022. Of them, 11 children were excluded from the analysis because they were hospitalized for reasons other than COVID-19. The demographic and clinical characteristics of the remaining 128 children in this study are shown in Table 1. The mean age was 3.62 ± 4.13 years, and 94 (73.4%) of them were younger than five years old. Half of the patients were female. Fever as the solitary symptom was the most common manifestation in young infants <3 months and accounted for 14 (63.6%) of 22 children. In the elder

Table 1 Demographics and clinical characteristics of 128 hospitalized children with COVID-19 of different age groups during the early omicron variant epidemic wave in Taiwan, April 1, 2022, to May 31, 2022.

Parameters	Hospitalized children with laboratory-confirmed COVID-19				
	Total N = 128	<3 months N = 22	3 months–4 years N = 72	5–11 years N = 29	12–17 years N = 5
Demographics					
Age in years (mean ± SD)	3.62 ± 4.13				
Female gender, n (%)	64 (50.0)	12 (54.5)	31(43.1)	19 (65.7)	2 (40.0)
Clinical syndromes					
Fever, n (%)	120 (93.7)	22 (100)	70 (97.2)	24 (82.7)	4 (90)
Fever as the solitary symptom, n (%)	18 (14.1)	14 (63.6)	4 (5.56)	0	0
Febrile seizure, n (%)	20 (15.7)	0	18 (25.0)	2 (6.90)	0
Breakthrough seizure	4 (3.13)	0	2 (2.78)	2 (6.90)	0
Encephalitis, n (%)	9 (7.03)	0	4 (5.56)	4 (13.7)	1 (20.0)
Croup syndrome, n (%)	14 (10.9)	1 (4.55)	13 (18.0)	0	0
Pneumonia, n (%)	6 (4.69)	0	3 (4.17)	2 (6.90)	1 (20.0)
Bronchiolitis, n (%)	2 (1.56)	0	2 (2.78)	0	0
Gastroenteritis, n (%)	5 (3.91)	0	3 (4.17)	2 (6.90)	0
Rhabdomyolysis, n (%)	4 (3.13)	0	0	4 (13.7)	0
Comorbidities	27 (21.3)	0	12 (16.7)	12 (41.4)	3 (60.0)
Neurologic comorbidities, n (%)	10 (7.81)	0	5 (6.94)	5 (17.2)	0
Managements					
Remdesivir, n (%)	33 (25.7)	0	18 (25.0)	13 (44.8)	3 (60.0)
Steroid, n (%)	27 (21.1)	0	21 (29.2)	6 (20.7)	1 (20.0)
Inotropic agents, n (%)	4 (3.12)	0	2 (2.77)	2 (6.89)	0
Intensive care, n (%)	16 (12.5)	0	7 (9.72)	7 (24.1)	2 (40.0)
Hospital stays in days, mean ± SD	5.56 ± 3.15	4.45 ± 0.67	5.53 ± 3.16	6.55 ± 4.13	5.20 ± 1.30
In hospital death, n (%)	2 (1.56)	0	0	2 (6.90)	0

Abbreviations: SD, standard deviation.

infants and toddlers aged 3 months to 4 years, febrile seizure (25%) and croup syndrome (18%) were the common manifestations. Approximately one-fifth (21.1%) of children had comorbidity, including complex neurological comorbidity in 7.9% of 128 patients. The mean hospital stay was 5.6 ± 3.15 days. Of 128 children, 16 (12.5%) required critical care, 4 (3.12%) had decompensated shock requiring inotropic support, and 2 (1.56%) cases in the age group 5—11 years died with fulminant encephalitis.

Characteristic of COVID-19—associated acute encephalitis (Table 2)

Of 128 children, thirty-three (25.7%) had neurological manifestations, including febrile seizure (20, 15.5%), encephalitis (9, 7.03%), and breakthrough seizure (4, 3.13%). When respectively compared to children with febrile seizure, croup syndrome, and fever as the solitary symptom, the children with encephalitis had significantly greater ages ($P < .05$ for all comparisons), and tended to have higher rates of ICU admissions, requirement of inotropic support, longer duration of hospital stays and in hospital death. The seizure episode was a common manifestation in children with encephalitis and often occurred on the first day of disease onset. The multivariable analyses disclosed that seizure ($P = .013$) and hypotension ($P = .008$) were the two significant factors independently associated with an increased risk of encephalitis.

Factors associated with unfavorable outcome of COVID-19—associated encephalitis (Table 3)

Three of nine cases with encephalitis had unfavorable outcomes, and two of them died. Cases with unfavorable outcomes showed lower levels of consciousness (median, 9.0 points vs. 14.5 points, $P = .020$) and more profound shock (systolic blood pressure, 77.0 mmHg vs. 113.5 mmHg, $P = .002$) and higher C-reactive protein level (6.19 mg/L vs. 0.77 mg/L, $P = .029$) than those with favorable outcomes. The values of inflammation markers including ferritin, and D-dimer were greater in cases with unfavorable outcomes compared to those with favorable, though of no statistical significance (Table 3).

Virus lineages

The spike sequences were available for 18 children, including 9 patients with encephalitis and 9 patients with non-encephalitis (Table 4). BA.2.3.7 with K97E mutation was the dominant omicron sublineage and accounted for 8 (88.9%) and 7 (77.7%) cases, respectively, of encephalitis and non-encephalitis ($P = 1.000$, Fisher's exact test).

Discussion

Results from the current cohort demonstrated several essential findings in evaluating neurologic manifestations in children with COVID-19 during the omicron BA.2.3.7 wave

Table 2 Comparison of clinical characteristics between children with encephalitis and those with other COVID-19 associated clinical syndromes.

Parameter	Encephalitis N = 9	Febrile seizure N = 20		Croup syndrome N = 14		Fever as the solitary symptom N = 18		*P*
			P1		P2		P3	
Symptoms/Signs								
Fever, n (%)	7 (77.8)	20 (100)	.089	14 (100)	.142	18 (100.0)	.103	.112
Cough, n (%)	2 (22.2)	11(55)	.130	14 (100)	<.001	0 (0)	.103	.481
Vomiting, n (%)	4 (44.4)	4 (20.0)	.209	4 (28.6)	.657	0 (0)	.007	.035
Seizure, n (%)	8 (88.8)	20 (100.0)	.310	0 (0)	<.001	0 (0)	<.001	<.001
Hypotension, n (%)	3 (33.3)	0 (0)	.023	1 (7.1)	.260	0 (0)	.029	<.001
Demographics								
Age in years, mean ± SD	6.16 ± 3.60	2.75 ± 1.95	.023	1.29 ± 0.92	.003	0.23 ± 0.22	.001	<.001
Male gender, n (%)	6 (66.7)	11 (55.5)	.694	7 (50.0)	.669	7 (38.9)	.236	.557
Comorbidities, n (%)	3 (33.3)	3 (15.0)	.339	2 (14.3)	.343	1 (5.6)	.093	.376
Neurologic comorbidities, n (%)	1 (11.1)	0 (0)	.310	1 (7.1)	1.000	0 (0)	.333	.332
Laboratory values								
WBC in 10^9/L, mean ± SD	5.32 ± 2.80	6.99 ± 2.15	.090	9.48 ± 4.71	.028	5.93 ± 2.26	.546	.099
CRP in mg/L, mean ± SD	4.27 ± 4.42	3.97 ± 4.46	.876	9.08 ± 7.66	.124	2.09 ± 2.03	.219	.397
Hospital stays in days, mean ± SD	7.33 ± 2.44	5.00 ± 0.97	.022	6.57 ± 4.73	.662	4.44 ± 0.61	.008	.016
Intensive care, n (%)	6 (66.7)	0 (0)	<.001	3 (21.4)	.077	0 (0)	<.001	<.001
Inotropic support, n (%)	3 (33.3)	0 (0)	.023	1 (7.14)	.260	0 (0)	.029	<.001
In hospital death, n (%)	2 (22.2)	0 (0)	.089	0 (0)	.142	0 (0)	.103	.008

P1, *P2* and *P3* were calculated by comparison of the indicated syndrome and encephalitis; *P* was calculated by comparison of cases with encephalitis versus those with COVID-19 syndromes other than encephalitis. The Fisher' exact test was applied to calculate the categorial variables in this Table.
Abbreviations: SD, standard deviation; CRP, C-reactive protein.

Table 3 Comparison of clinical features and laboratory parameters in children with COVID-19 associated encephalitis according to the outcomes.

Parameter	Unfavorable outcomes		Favorable outcome		*P*
	N		N		
Age in years, median (range)	3	6.5 (3.1—7.3)	6	5.7 (0.9—12.0)	.776
Gender, n (%)	3	3 (100.0)	6	3 (50)	.464
Comorbidities, n (%)	3	2 (66.7)	6	1 (16.6)	.226
Seizure, n (%)	3	3 (100.0)	6	5 (83.3)	1.000
occurrence within 24 h of fever onset, n (%)	3	3 (100.0)	5	2 (40)	.196
Consciousness change, n (%)	3	3 (100.0)	6	6 (100.0)	…
Glasgow coma scale, median (range)	3	9.0 (3—10)	6	14.5 (9—15)	.020
GCS <8, n (%)	3	2 (66.7)	6	0 (0)	.083
Systolic blood pressure in mmHg, median (range)	3	77.0 (67—77)	6	113.5 (97—137)	.002
Hypotension, n (%)	3	3 (100.0)	6	0 (0)	.012
White blood cell count in 10^9/L, median (range)	3	8.3 (1.2—10.5)	6	4.6 (3.5—6.2)	.549
Hemoglobin in g/dL, median (range)	3	12.4 (10.6—13.1)	6	13 (10.5—14.4)	.389
Platelet in 10^9/L, median, (range)	3	433.0 (303.0—542.0)	6	234.5 (171.0—382.0)	.050
C-reactive protein in mg/L, median (range)	3	6.19 (5.50—13.29)	6	0.77 (0.50—5.88)	.029
Lactate dehydrogenase in U/L, median (range)	3	283.5 (182—319)	6	283.5 (182—319)	.294
Ferritin in ng/mL, median (range)	3	4578 (154—9003)	6	55.9 (36.3—138)	.495
D-dimer in ng/mL, median (range)	3	2666 (1154—1000)	6	528 (224—789)	.273

Fisher's exact test was applied to calculate the categorial variables in this Table.

Table 4 Distribution of virologic sublineages of omicron in pediatric COVID-19 with and without encephalitis.

Lineage/mutation profile	Amino acid alterations in S protein[a]	Encephalitis N = 9	Non-encephalitis N = 9
BA.2.3.7			
Profile 1	T19I, 24-26del, A27S, **K97E**, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K, **G1251V**	5	2
Profile 2	**K97E, G1251V (absent)**	3	4
Profile 3	**K97E, S255F (new), G1251V (absent)**	0	1
BA.2.3	T19I, 24-26del, A27S, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K	1	1
BA.1	A67V, 69-70 del, T95I, G142D, 143-145 del, 211 del, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F	0	1

[a] Mutations are completely listed in Profile 1 of BA.2.3.7. Important mutation (K97E) and mutations different from profile 1 are highlighted in bold in profiles 2 and 3.

of the pandemic. Firstly, most COVID-19-associate encephalitis occurred in school-age children with a mean age of 6.16 years, not only in those with underlying comorbidities but also in previously healthy children. Secondly, children with COVID-19-associate encephalitis were more commonly presented with seizure and hypotension than those without encephalitis. Furthermore, children with COVID-19-associated encephalitis could develop unfavorable outcomes, with higher rates of mortality and PICU admission and a prolonged hospital stay. Indeed, all the children with syndromes other than encephalitis survived to discharge and left no sequelae. Encephalitis cases may rapidly deteriorate to shock or death within the first few days of disease onset, especially in those with elevated levels of specific inflammation markers, including LDH, ferritin, and D-dimer. The same sublineage BA.2.3.7 with K97E mutation on spike protein was also identified in cases with syndrome other than encephalitis. The role of the viral factors, including the novel mutation K97E in the surge of the BA.2.3.7-associated encephalitis, remained unclear and required further study.

Respiratory illness is the most distinctive clinical spectrum of SARS-CoV-2 infections in adult populations. Neurologic manifestations, although not as common as

respiratory syndromes, can be observed in some patients with acute COVID-19, including in the pediatric population.[23] Nevertheless, encephalitis was rarely reported in children with COVID-19 requiring hospitalization.[1,24] The observation that encephalitis accounted for 7.1% in this pediatric cohort was unusual. The plausible reasons for the high rate of encephalitis in this cohort included the naïve immunity to SARS-CoV-2 in the Taiwanese population and genetic susceptibility. Indeed, by the start of the omicron wave, most children in Taiwan remained unvaccinated and entirely naïve to SRSR-CoV-2. Since the onset of the COVID-19 pandemic in early 2020, the Taiwan government has implemented stringent social distancing policies, including universal masking, contact tracing, intermittent business closures, and territory-wide school suspensions. These measures were associated with the lowest number of COVID-19 cases in Taiwan during the global pandemic caused by the variants of concern preceding omicron.[25] Most children were uninfected and did not acquire immunity from previous infections. Notably, the risks of neurologic complications had been reported higher for omicron BA.2 than hospitalizations occurring during the delta-predominant period.[26] Further, acute encephalitis is a well-known severe complication of virus infections predominantly described in Asian children, such as enterovirus and influenza, suggesting genetic susceptibility to this devastating disease.[27,28] A recent study among Hong Kong children showed that omicron BA.2 can be more neuropathogenic than influenza.[26] Given its severe consequences, encephalitis must be kept in mind when dealing with pediatric COVID-19, especially in the Asian population.

In this cohort, children with COVID-19-associated encephalitis had significantly worse outcomes than those without encephalitis. More than one-third of patients admitted to the PICU had encephalitis, and 22.2% of them died in the hospital. This finding is consistent with an earlier meta-analysis, which showed that hospitalized children with encephalitis as a complication of COVID-19 have greater COVID-19 disease severity, including greater intensive resource use and mortality.[29] Previous studies have demonstrated that the mortality rate of patients with encephalitis as a complication of COVID-19 was 13.4%, almost four times higher than the rate (3.4%) in the general population with COVID-19.[30] Results from the current study further suggested that children in school age, irrespective of coexisting conditions, were susceptible to this devastating disease. To our knowledge, this was the first study to identify the demographic factors of increased risk of developing COVID-19 encephalitis in children. Our findings highlight the importance of immunization against SARS-CoV-2 in all children, irrespective of underlying conditions, which remained the best and most helpful strategy to avoid the severe complication of COVID-19.

The clinical picture of COVID-19—associated encephalitis was different in pediatric and adult series. In adults, the encephalitis was reported to occur at an average interval of 14.5 days from diagnosis of COVID-19.[31] In this cohort, the seizures occurred in children within the first 1—4 days after fever onset. In those with unfavorable outcomes, the seizures were followed by rapid neurological deterioration and hemodynamic instability within days or even hours.[16] The rapidly developed course posed a significant challenge to primary care clinicians in the identification of the devastating disease as the simple febrile seizure was common in the general pediatric population. Data from our study indicated that a depressed level of consciousness and low blood pressure were linked to a higher likelihood of rapid deterioration in COVID-19 patients. In line with previous studies, our research emphasized the need for caregivers to closely monitor clinical symptoms in children with COVID-19 and provide prompt, aggressive treatment to those showing the concerning signs.

The strengths of the study included comprehensive information regarding the clinical characteristics and outcomes of acute encephalitis in COVID-19 children and examining the clinical features and virologic lineages. We also explored demographic, and clinical predictive factors to early recognition of encephalitis as a potentially severe complication of COVID-19 in pediatric patients. The age factor of increased risk of encephalitis identified in this study may also be used to prioritize immunization in children. There were limitations in this study. First, the retrospective nature of the study did not allow us to include all the laboratory parameters of interest. Second, the data from the single center might not be generalized to the other population. In addition, only 18 of 128 children had spike sequencing results, and the role of viral factors, needs to be further investigated.

In conclusion, encephalitis was a severe complication of pediatric COVID-19 and was associated with high incidences of seizure activities and hemodynamic instability. Children at school age, irrespective of underlying conditions, might be more susceptible to this devastating disease than children of other age groups. Children who experience seizures, altered consciousness, and hypotension were at a higher risk of unfavorable outcomes. Early recognition of at-risk children followed by prompt medical intervention may help improve the outcomes in children with COVID—19—associated encephalitis. Immunization against SARS-CoV-2 remained one of the crucial measures to protect this vulnerable population.

Conflicts of interest

The authors declared no conflicts of interest.

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