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RESEARCH ARTICLE

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Clinical characteristics of unvaccinated or incompletely vaccinated children with neurological manifestations due to SARS-CoV-2 Omicron infection

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Abstract

Omicron generally causes milder disease than previous strains of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), especially in fully vaccinated individuals. However, incompletely vaccinated children may develop Omicron-related complications such as those affecting the central nervous system. To characterize the spectrum of clinical manifestations of neuro-COVID and to identify potential biomarkers associated with clinical outcomes, we recruited 15 children hospitalized for Omicron-related neurological manifestations in three hospitals in Hong Kong (9 boys and 6 girls aged 1–13 years). All were unvaccinated or incompletely vaccinated. Fourteen (93.3%) were admitted for convulsion, including

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benign febrile seizure ($n = 7$), complex febrile seizure ($n = 2$), seizure with fever ($n = 3$), and recurrent breakthrough seizure ($n = 2$), and the remaining nonconvulsive patient developed encephalopathic state with impaired consciousness. None of the seven children with benign febrile seizure and six of eight children with other neurological manifestations had residual deficits at 9-month follow-up. SARS-CoV-2 RNA was undetectable in the cerebrospinal fluid (CSF) specimens of seven patients who underwent lumbar puncture. Spike-and-wave/sharp waves affecting the frontal lobes were detected in four of seven (57.1%) patients who underwent electroencephalogram. Children with Omicron-related neurological manifestations had significantly higher blood levels of IL-6 ($p < 0.001$) and CHI3L1 ($p = 0.022$) than healthy controls, and higher CSF levels of IL-6 ($p = 0.002$) than children with non-COVID-19-related febrile illnesses. Higher CSF-to-blood ratios of IL-8 and CHI3L1 were associated with longer length of stay, whereas higher ratios of IL-6 and IL-8 were associated with higher blood tau level. The role of CSF:blood ratio of IL-6, IL-8, and CHI3L1 as prognostic markers for neuro–COVID should be further evaluated.

KEYWORDS
children, COVID-19, neurological, Omicron, SARS-CoV-2, seizure

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has greatly affected the physical and mental wellbeing of children globally.[1,2] The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant was first detected in South Africa in November 2021 and quickly became the predominant variant worldwide.[3,4] With its exceptionally high immunoevasiveness and transmissibility,[5,6] the number of Omicron-infected patients has caused significant disease burden in many countries despite the virus' comparatively lower clinical severity than previous variants. Among the pediatric population, the number of Omicron-infected children has surpassed the total number of COVID-19 cases caused by previous variants.[7]

While Omicron generally causes less severe disease than wild-type and previous variants of SARS-CoV-2, a number of studies have shown disproportionately high hospitalization rates among young children.[8–10] Of particular concern among hospitalized Omicron-infected children is the development of neurological complications. Compared to other common respiratory viruses such as influenza and parainfluenza viruses, a significantly higher proportion of unvaccinated hospitalized Omicron-infected children in Hong Kong developed neurological complications (15.0% for Omicron vs. 8.4% for influenza viruses and 7.7% for parainfluenza viruses).[11] In South Africa, 31.1% of hospitalized Omicron-infected children developed seizures as compared to 8.5% of those who were infected by preceding SARS-CoV-2 strains.[10] In a large population-based study involving 152 754 patients, COVID-19 was associated with increased risk of seizures compared to influenza. The hazard ratio was greater in patients under 16 years.[12] Although it is possible that some of the mild or asymptomatic cases of Omicron infection in the community might have been underdiagnosed, these findings indicate that neurological complications can occur in children with moderate to severe Omicron infection. It remains unclear whether the neurological manifestations might be caused by neuroinvasion by SARS-CoV-2 or due to neuroinflammatory responses as a result of the cytokine release syndrome.[13,14]

We have previously shown that Omicron exhibits enhanced replication in human forebrain and midbrain organoids.[15] A recent study also reported that in addition to Omicron, other SARS-CoV-2 variants also frequently spread to and within the central nervous system.[16] On the contrary, a small case series of five COVID-19 children with critical neurological manifestations showed that none of their cerebrospinal fluid (CSF) specimens were positive for SARS-CoV-2 RNA by reverse transcription-polymerase chain reaction (RT-PCR). Three of the five children had markedly raised blood IL-6 level,

suggesting that the severe neurological symptoms might be related to immunodysregulation rather than direct neuroinvasion.[17] Immunologically, cytokines such as IL-6 and IL-8 are pivotal in the generation of acute systemic inflammatory response.[18,19] A skewed cytokine profile towards IL-6 and IL-8 was associated with cardiac dysfunction in children with multisystem inflammatory syndrome (MIS-C).[20] However, another study showed that plasma IL-6 level failed to discriminate children with MIS-C with or without shock.[21] Adults with neuro-COVID were found to have elevated blood and CSF IL-6 and IL-8 levels, but only the CSF IL-8 level correlated with disease severity.[22] Similarly, it is possible that the blood IL-6 and IL-8 levels may not accurately reflect disease severity in children with neuro-COVID. We hypothesized that the inflammatory markers in CSF rather than the level of cytokines in blood were better correlates of the disease severity and outcome of children with neuro-COVID. In addition, as neuroinflammatory markers such as chitinase-3 like-protein-1 (CHI3L1) and soluble triggering receptor expressed on myeloid cells 2 (sTREM-2) are closely associated with neuroinflammation and neurodegenerative diseases such as Alzheimer's disease,[23,24] we investigated whether their blood or CSF levels were correlated with changes in neuronal activities manifested as seizures as well as neuronal damage in our patients. To better define the spectrum of clinical manifestations and to identify potential biomarkers associated with the clinical outcomes of children with Omicron-related neurological complications, we recruited children who were hospitalized for Omicron-related neurological manifestations during the Omicron wave in Hong Kong.[25] We also conducted a systematic review on the clinical features and investigation findings of children with Omicron-related neurological manifestations reported in other areas.

2 | MATERIALS AND METHODS

2.1 | Ethics approval and study subjects

Ethics approval was obtained from the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 20-292 and UW 21-583), Hong Kong East Cluster-Research Ethics Committee (HKECREC-2020-055), and Kowloon West Cluster Research Ethics Committee [KW/FR-20-086(148-10)]. Children aged 0 to <18 years hospitalized in the pediatric units of three public hospitals (Queen Mary Hospital, Princess Margaret Hospital, and Pamela Youde Nethersole Eastern Hospital) in Hong Kong during the city's Omicron wave between February 1, 2022 and June 30, 2022 who developed COVID-19 with neurological manifestations were recruited with consent taken from their legal guardians.

Children without history of SARS-CoV-2 infection and neurological diseases were recruited from the community or the general pediatric clinic as control subjects. Children with chronic medical illnesses, genetic disorders, or on long-term medications were also excluded. Blood specimens were collected from the control subjects for measurement of IL-6, IL-8, CHI3L1, sTREM-2, and Tau levels. To investigate whether children with neuro-COVID had higher level of inflammatory markers in comparison with children with non-COVID febrile illnesses, archived sterile CSF specimens obtained from patients treated at the general pediatrics ward (i.e., age >1 month to <18 years) as part of their sepsis workup due to non-COVID-19 acute febrile illnesses were used. The CSF levels of IL-6, IL-8, CHI3L1, and Tau were tested.

2.2 | Case definition

The diagnosis of COVID-19 was confirmed by RT-PCR of their respiratory tract specimens using LighMix® E-gene kit as previously described.[26] Except for one patient with missing data, all other patients were tested negative for common respiratory viruses, including influenza viruses, parainfluenza viruses, adenoviruses, enteroviruses/rhinoviruses, and respiratory syncytial virus by multiplex PCR using BioFire® FilmArray RP2.1 plus (bioMérieux). Neurological manifestations in this study included one or more of the following: (i) encephalopathic state with altered mental status lasting ≥24 h, (ii) generalized or partial seizures with or without pre-existing history of epilepsy or seizure, (iii) new onset of focal neurological signs, (iv) CSF white blood cell count ≥5/mm^3, (v) abnormality of brain parenchyma on neuroimaging suggestive of acute encephalitis or meningitis, and (vi) abnormality on electroencephalography (EEG) consistent with encephalitis or meningitis. Clinical characteristics such as the type and severity of neurological symptoms, length of hospitalization, Pediatric Cerebral Performance Category (PCPC) Scale which reflects the cognitive impairment of children postadmission to PICU and residual neurological deficits, as well as investigation findings including blood tests, EEGs, and neuroimaging studies were obtained via electronic patient chart review. All EEGs were interpreted by a pediatric neurologist and the magnetic resonance imaging studies of the brain were interpreted by a radiologist.

The definition of the different types of seizures were defined as follows in this study: (i) benign febrile seizure: simple febrile convulsions manifesting as nonfocal seizures with fever in children aged 6 months to 5 years who had no known history of epilepsy; (ii) complex febrile convulsion in pediatric patients in children aged 6 months to 5 years (iii) seizure with fever: seizures associated with fever in children aged <6 months or ≥6 years, and (iv) epilepsy with breakthrough seizure: recurrence of seizure during the episode of Omicron infection in children with known history of epilepsy.

2.3 | Viral load, inflammatory markers, and neuronal markers analyses

CSF and blood specimens were obtained at Day 0 of the illness (i.e., on the same day with the first positive RT-PCR result for SARS-CoV-2) for SARS-CoV-2 RNA detection (CSF) and/or inflammatory and

neuronal markers (CSF and blood) evaluation. SARS-CoV-2 RNA detection was performed using our established protocol.[27] Briefly, 200 µL of each CSF specimen was subjected to total nucleic acid extraction using EZ1 Virus Mini Kit v2.0 (QIAGEN), with an elution volume of 60 µL. Real-time RT-PCR assays were performed using primers and probes targeting RdRp/helicase and nucleocapsid genes of SARS-CoV-2, and reagents of QuantiNova Probe RT-PCR kit (QIAGEN) according to manufacturer's instructions. RT-PCR was run in a LightCycler 480® Instrument II (Roche), with the thermocycling condition: 45°C for 10 min and 95°C for 5 min, followed by 45 cycles of 95°C for 5 s and 55°C for 30 s. As IL-6 and IL-8 levels had consistently been found to be perturbed in acute inflammatory response as well as MIS-C,[19,28] the blood and CSF levels of IL-6 and IL-8 were measured using ELISA MAX™ Deluxe Set Human IL-6 and ELISA MAX™ Deluxe Set Human IL-8 (BioLegend). Being markers of neuroinflammation[29] as well as biomarkers for Alzheimer's disease,[23,24] the blood and CSF chitinase-3 like-protein (CHI3L1) and sTREM-2 were measured using Human chitinase-3-like-1QUantikine ELISA Kit (R&D Systems) and Human TREM2 DuoSet ELISA kit (R&D Systems), respectively. Briefly, 96-well microplates were blocked with 1% bovine serum albumin and coated with the capture antibodies. The capture antibodies included anti-human IL-6, anti-human IL-8, anti-human TREM2, anti-human CHI3L1, and anti-human Tau antibodies. One hundred microliters of samples, standard or diluent were incubated with the capture antibodies for 2 h at room temperature. After three washes with phosphate-buffered saline supplemented with 0.05% Tween-20 (PBST) buffer, a biotinylated anti-human IL-6, anti-human IL-8, anti-human TREM2, anti-human CHI3L1, or anti-human Tau antibody was added to each well and the plate was incubated for 2 h at room temperature. After three washes with PBST, 100 µL of streptavidin-horseradish peroxidase was added to each well. The plate was then incubated for 20 min at room temperature in the absence of light, followed by three washes with PBST. After that, 100 µL of substrate solution was added to each well and the plate was incubated for 20 min at room temperature in the absence of light. Fifty microliters of stop solution were then added to each well to stop the reaction. Then, the detection was performed using a Multiskan™ FC Microplate Photometer set to 450 nm (Thermo Fisher Scientific).

Primary outcomes were the differences of IL-6, IL-8, CHI3L1, and sTREM-2 between cases and control subjects. Correlational analyses were conducted to investigate the associations of these inflammatory markers and clinical outcomes of Omicron-infected children with neurological manifestations. Secondary outcomes included how viral load affected the level of inflammatory markers. The associations between the inflammatory, neuroinflammatory markers, and Tau levels were investigated. The blood and CSF Tau protein levels, a marker for axonal or neuronal damage, were measured using Human Tau ELISA kit (MyBioSource). All measurements were performed according to manufacturer's protocol and in duplicate. Case subjects were also tested for RANBP2 mutation as children with the dominant missense mutation in RANBP2 are prone to acute necrotizing encephalopathy.[30]

2.4 | Statistical analysis

Independent sample *t*-tests or chi-square tests were performed to compare the clinical characteristics during hospitalization and the levels of inflammatory, neuronal, and biological markers in blood and CSF between Omicron-infected patients and control subjects, and between patients with simple febrile convulsion and those with other conditions. If the equal variance was not assumed, nonparametric test would be performed. Pearson correlations were performed to investigate the associations between the ratio of inflammatory, neuronal markers and the hospitalization status, clinical characteristics, or the total number of seizures. Missing values were excluded. Pairwise and false discovery rate adjustment were performed for multiple comparisons. All statistical tests were performed using SPSS version 28.

2.5 | Systematic review

A systematic review using the terms "Omicron" AND (Neurology OR Seizure OR Epilepsy OR Encephalitis OR Encephalopathy) AND (Child OR children OR pediatric OR pediatric) and their synonyms to search for related studies in PubMed from January 11, 2020, to March 31, 2023, was conducted. The complete search string was included in the appendix. Studies that reported cases of Omicron-related neurological complications were included in this review. Studies that did not report patient details at the individual level were excluded. Figure 1 shows the flow chart of the systematic review according to the PRISMA guideline.

3 | RESULTS

3.1 | Clinical characteristics

During the study period, we successfully recruited 15 children who fulfilled the inclusion criteria to join this study. These included nine boys and six girls with a mean age of 4.92 ± 3.87 years. Their demographic information was summarized in Table 1. Among these 15 patients, 14 were unvaccinated and 1 has received a single dose of mRNA vaccine [Comirnaty (BioNTech) by Pfizer]. One-third (n = 5) of the patients were admitted to PICU and 6 (40%) of them had history of neurological diseases or developmental disorders. Fourteen (93.3%) of them were admitted for convulsion and the remaining nonconvulsive patient (6.7%) was admitted for encephalopathic state with impaired consciousness. All of the 14 patients admitted for convulsion had single or multiple (up to 4) episodes of generalized tonic or tonic-clonic seizures. Seven had benign febrile seizure, two had complex febrile seizure, three had seizure(s) with fever, and two had recurrent breakthrough seizures. These two patients with recurrent breakthrough seizures had underlying syndromal

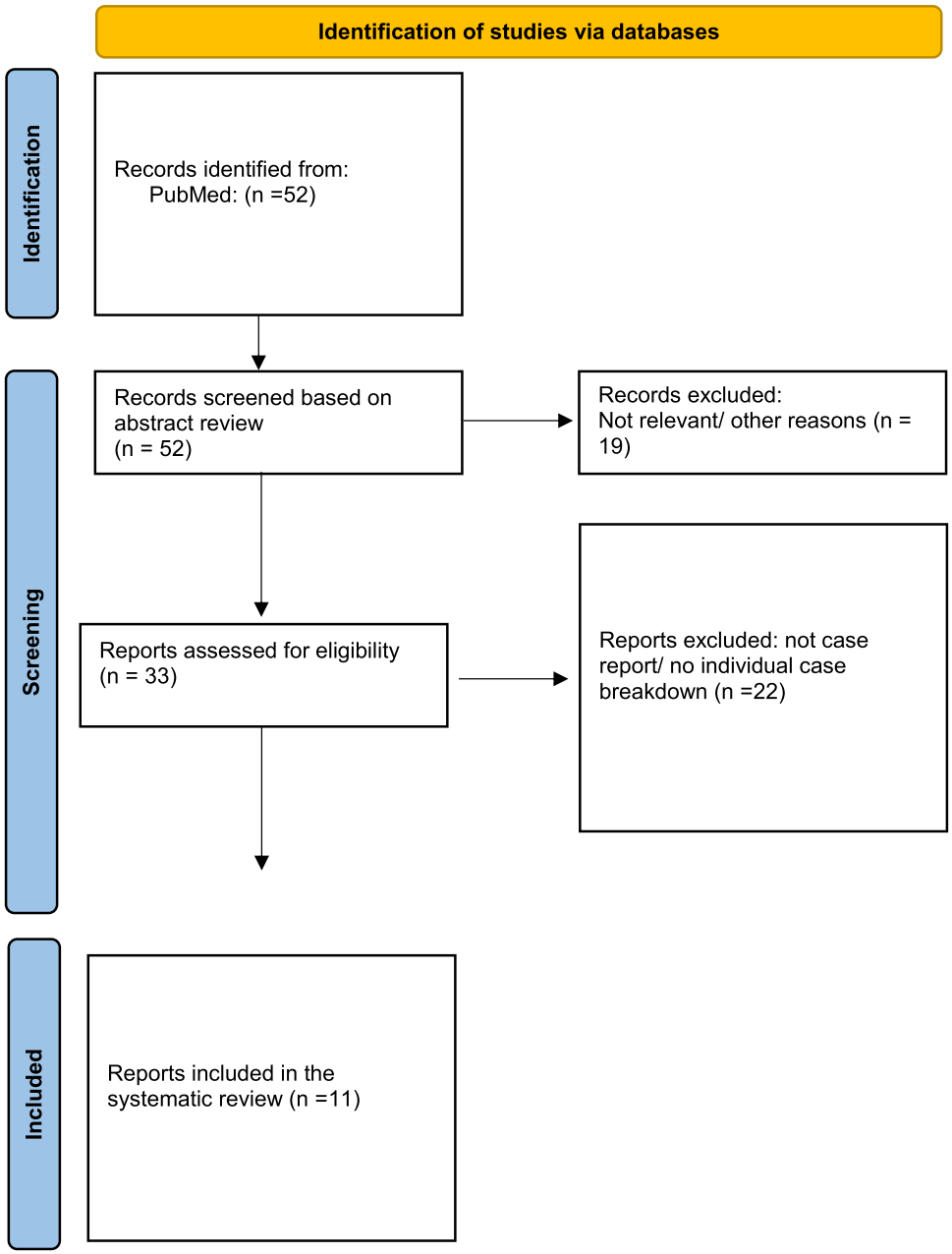

FIGURE 1 The systematic review search flow chart. The full searching string using PubMed on March 30, 2023 was as below: "Omicron"[All Fields] AND ("neurology*"[All Fields] OR "seizure*"[All Fields] OR ("epilepsie"[All Fields] OR "epilepsy"[MeSH Terms] OR "epilepsy"[All Fields] OR "epilepsies"[All Fields] OR "epilepsy s"[All Fields]) OR "epileptic*"[All Fields] OR ("encephalities"[All Fields] OR "encephalitis"[MeSH Terms] OR "encephalitis"[All Fields]) OR ("brain diseases"[MeSH Terms] OR ("brain"[All Fields] AND "diseases"[All Fields]) OR "brain diseases"[All Fields] OR "encephalopathies"[All Fields] OR "encephalopathy"[All Fields]) OR "Acute Necrotizing Encephalopathy"[All Fields] OR "Acute Necrotizing Encephalopathy"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields] OR ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s" [All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]) OR "pediatric*"[All Fields] OR ("pediatrics"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "pediatric"[All Fields] OR "pediatric"[All Fields]).

disorders (i.e., Dravet syndrome or tuberous sclerosis) and one of them developed status epilepticus. The only non-convulsive patient who presented with impaired consciousness had evidence of acute necrotizing encephalitis. In terms of clinical progress and outcome, the median duration of hospitalization was 3 days (1–27 days) for these 15 patients, including 4 who required admission to the pediatric intensive care unit. None of the seven children with benign febrile seizure had residual neurological deficits at 9-month follow-up, whereas 6 of the other 8 children with other neurological manifestations had residual deficits such as worsening seizure control, abnormal sensorium, and/or abnormal muscle weakness or tone.

TABLE 1 Clinical characteristics of pediatric patients infected with Omicron.

ID	Age (years)	Sex	Omicron subtype	Significant past medical history	Vaccination status	Neurological manifestation	PICU	No. of seizures	PCPC	Residual deficits	EEG	Neuroimaging	LOS
1	1.8	M	BA.2.2	Febrile convulsion	Unvaccinated	Benign febrile seizure	Yes	1	1	No	NA	NA	8
2	7.6	F	BA.2.2	Dravet syndrome, moderate ID	Unvaccinated	Breakthrough seizure	No	3	4	Yes	NA	NA	10
3	8.9	M	NA	None	Unvaccinated	Seizure with fever	No	5	2	Yes	Sharp slow wave over bilateral frontal region	NA	3
4	13.3	F	BA.2.2	None	1 dose BioNTech	Seizure with fever	Yes	3	1	No	Abnormally suppressed, frontocentral predominance dominant rhythm, replaced the normal posterior dominant rhythm	NA	3
5	2.6	M	BA.2.2	ASD, GDD	Unvaccinated	Benign febrile seizure	Yes	3	1	No	NA	Normal CT	3
6	2.9	F	BA.2.10.1	None	Unvaccinated	Benign febrile seizure	No	1	1	No	NA	NA	2
7	5.2	M	BA.2.10.1	Febrile convulsion	Unvaccinated	Complex febrile seizure	No	3	2	Yes	Frontal predominance sharp slow wave (3 Hz)	NA	2
8	2.2	M	BA.2.2	None	Unvaccinated	Benign febrile seizure	No	1	1	No	NA	NA	1
9	4.1	M	NA	Tuberous sclerosis, GDD	Unvaccinated	Epilepsy with breakthrough seizure (status epilepticus)	No	3	3	Yes	No definitive epileptic activity	MRI brain: features of tuberous sclerosis	3
10	0.9	M	BA.2.2.1	None	Unvaccinated	Benign febrile seizure	No	1	1	No	NA	NA	2
11	1.3	F	BA.2.2	None	Unvaccinated	Benign febrile seizure	No	1	1	No	NA	NA	2
12	2.5	F	BA.2.2	Severe iron deficiency anemia	Unvaccinated	Complex febrile seizure	No	4	1	No	3 Hz spikes, with bifrontal predominance during drowsy & sleep states	Normal CT brain	1
13	1.7	M	BA.2.2	None	Unvaccinated	Benign febrile seizure	No	1	1	No	NA	NA	1
14	8.1	F	BA.2.2	Guillain–Barre syndrome, pancreatitis	Unvaccinated	Encephalopathic state with impaired consciousness	Yes	0	3	Yes	Generalized symmetrical slowing	MRI brain: pattern of acute necrotizing encephalitis involving brainstem, basal ganglia and frontal, temporal, and parietal lobes.	27

TABLE 1 (Continued)

ID	Age (years)	Sex	Omicron subtype	Significant past medical history	Vaccination status	Neurological manifestation	PICU	No. of seizures	PCPC	Residual deficits	EEG	Neuroimaging	LOS
15	10.7	M	NA	None	Unvaccinated	Seizure with fever	Yes	0	3	Yes	Intermittent slow waves and spikes over bilateral posterior area. Intermittent spikes over frontal temporal area, more on the left side	Normal CT brain	8

Abbreviations: ASD, autism spectrum disorder; CT, computerized tomography scan; EEG, electroencephalogram; F, female; GDD, global developmental delay; ID, intellectual disability; IVIG, intravenous immune globulin; LOS, length of stay; M, male; MRI, magnetic resonance imaging; NA, not available; PCPC, pediatric cerebral performance category; PICU, pediatric intensive care unit.

3.2 | Investigation results

Regarding investigation results, EEG was performed for seven patients, with four of them (Patients 3, 7, 12, and 15) showing spike-and-wave/sharp waves affecting the frontal lobes (Figure S1). CT or MRI scans of the brain were performed for five patients. None except one demonstrated signs of acute new changes. The MRI brain scans of the patient who presented with encephalopathic state with impaired consciousness showed evidence of acute necrotizing encephalitis involving the brainstem, basal ganglia, and frontal, temporal, and parietal lobes. CSF samples were collected from seven patients. All seven CSF specimens showed elevated levels of Tau with six out of seven showed raised IL-6 in CSF despite being negative for SARS-CoV-2 by RT-PCR (Table 2). Similarly, the blood levels of IL-6 and CHI3L1 were elevated in 12 of the 15 patients. Independent *t*-tests showed that the patients had significantly higher levels of CHI3L1 (17 124.37 vs. 11 022.71, $p = 0.022$) in blood than control subjects, while nonparametric tests showed that the COVID–19 patients had higher levels of IL-6 in blood (19.31 vs. 2.84, $p < 0.001$) and CSF (74.44 vs. 5.26, $p < 0.001$) as well as higher levels of Tau in CSF (29.34 vs. 0.00, $p = 0.004$) than subjects with non-COVID, bacterial culture negative febrile illnesses (Figure 2; Table S1). Thirteen of the fifteen (87%) Omicron-infected children with neurological manifestations also had lymphopenia (mean lymphocyte count = 0.89, SD = 0.41, $p < 0.001$).None of the patients, including patient 14 who developed ANE, tested positive for the RANBP2 mutation which is associated with a higher risk of ANE.

Pearson's correlation was conducted to further investigate the correlation between the biomarkers and clinical characteristics of our Omicron patients (Table 3). Our results showed that patients' length of hospitalization was associated with higher CSF-to-blood ratio of IL-8 ($r = 0.889$, $p = 0.035$) and higher CSF-to-blood ratio of CHI3L1 ($r = 0.885$, $p = 0.032$). Moreover, patients' levels of tau in blood was correlated to higher CSF-to-blood ratio in IL-6 ($r = 0.917$, $p = 0.02$) and in IL-8 ($r = 0.953$, $p = 0.012$). An exploratory analysis of the correlation between other biomarkers and clinical characteristics was further shown in Table S2. In addition, a lower C_t value (higher viral load) was associated with a higher level of sTREM–2 in CSF ($r = -0.89$, $p = 0.034$).

3.3 | Systematic review

A total of 11 publications describing 46 pediatric patients with COVID-19–related neurological manifestations were included in the systematic review[17,31–40] (Table 4). Among the 46 patients, 19 (41.3%) were female and 27 (58.7%) were males. Their mean age was 4.52 ± 3.41 years (median, 3 years; range, 29 days to 14 years; interquartile range, 5.31 years). Among the 27 patients with reported length of stay in the hospital, the mean value was 5.26 ± 6.75 days (median, 3 days; range, 0–31 days; interquartile

TABLE 2 Blood and/or cerebrospinal fluid (CSF) parameters of pediatric patients infected with Omicron.

			Serum										Cerebrospinal fluid					
ID	Age	Sex	WCC	ANC	LYM	CRP	Protein	IL-6	IL-8	sTREM-2	CHI3L1	Tau	Protein	IL-6	IL-8	sTREM-2	CHI3L1	Tau
1	1.8	M	6.62	3.66	1.63	0.94	76	43.28	6.10	120.13	28 338.90	174.01	–	–	–	–	–	–
2	7.6	F	7.28	5.75	0.60	1.95	69	9.21	10.3	155.15	15 771.57	114.33	–	–	–	–	–	–
3	8.9	M	5.33	3.69	0.64	–	78	6.56	5.00	408.90	19 214.29	53.09	0.15	20.46	26.6	572.37	54 439.97	11.40
4	13.3	F	3.33	2.03	1.03	0.54	65	5.30	1.60	281.58	21 234.76	66.32	0.13	5.76	26.5	320.34	29 488.88	58.40
5	2.6	M	5.02	3.14	0.98	0.91	77	10.35	17.5	144.60	8395.89	44.08	0.29	27.81	53.6	675.61	19 678.61	75.70
6	2.9	F	8.28	7.01	0.51	0.41	66	24.13	1.50	0.00	14 499.48	174.39	–	–	–	–	–	–
7	5.2	M	5.60	3.97	0.83	0.65	69	–	2.70	0.00	14 109.56	23.18	<0.10	47.73	20.2	404.00	19 694.07	10.10
8	2.2	M	7.20	4.53	1.29	–	78	43.87	3.10	360.94	15 936.47	54.79	–	–	–	–	–	–
9	4.1	M	19.60	18.30	0.90	3.60	83	21.23	<0.10	375.57	17 409.10	79.99	–	–	–	–	–	–
10	0.9	M	11.32	8.60	1.58	<0.35	70	11.75	1.30	0.00	18 095.72	148.27	–	–	–	–	–	–
11	1.3	F	3.69	2.03	0.85	–	–	32.34	8.30	191.33	10 798.39	29.49	–	–	–	–	–	–
12	2.5	F	5.79	4.74	0.44	<0.35	69	33.75	5.90	119.60	19 802.27	95.74	<0.10	36.31	106.7	204.62	INF	40.90
13	1.7	M	6.33	4.75	1.27	–	71	20.19	4.20	48.36	16 420.90	110.53	–	–	–	–	–	–
14	8.1	F	2.23	1.68	0.46	<0.35	90	1.86	–	0.00	2891.03	68.62	0.25	22.54	13.10	422.05	15 957.08	8.90
15	10.7	M	14.28	12.81	0.36	1.54	70	6.56	1.60	0.00	33 947.23	183.51	0.15	360.46	134.00	485.30	49 879.57	INF

Note: Values are expressed in $\times 10^9$/L for WCC, ANC, LYM; in mg/dL for CRP; in g/L for protein; in pg/mL IL-6, IL-8, sTREM-2, CHI3L1, Tau.

Abbreviations: ANC, absolute neutrophil count; CHI3L1, chitinase-3 like-protein-1; CRP, C-reactive protein; IL-6, interleukin 6; IL-8, interleukin-8; INF, insufficient sample for laboratory testing; LYM, lymphocyte count; sTREM2, soluble triggering receptor expressed on myeloid cells 2; WCC, white cell count.

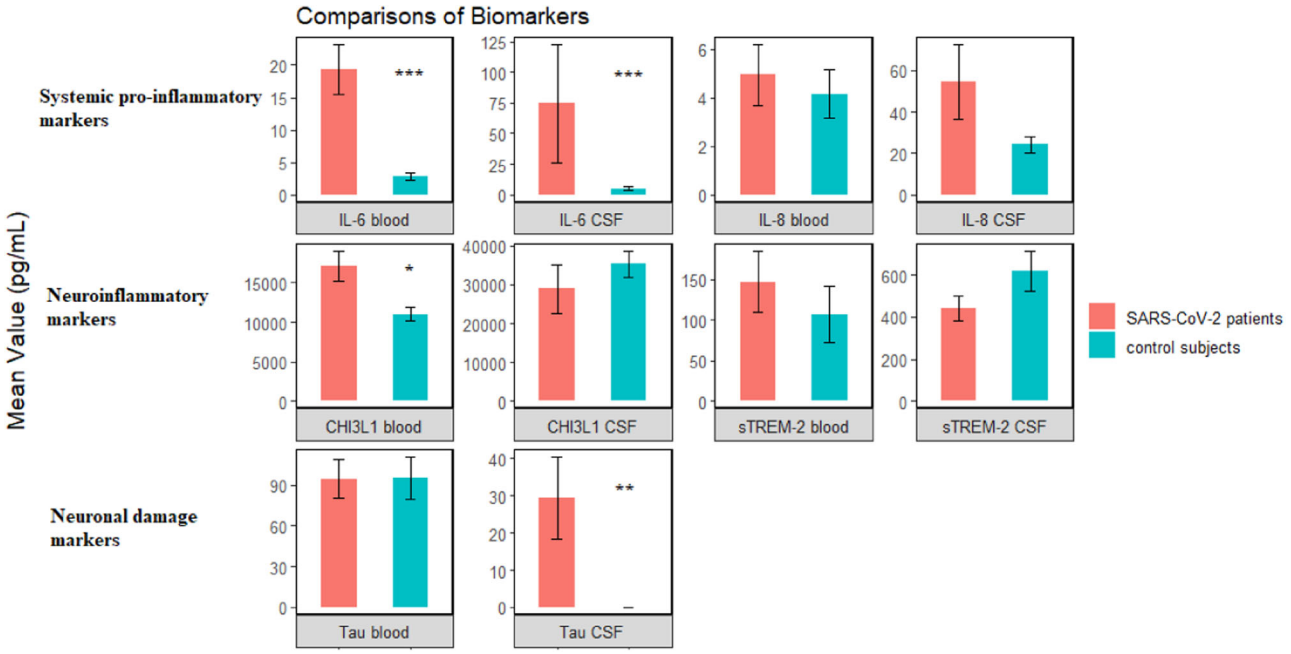

FIGURE 2 Comparison of inflammatory and neuronal markers between Omicron-infected patients and control subjects. CHI3L1, chitinase-3 like-protein-1; IL-6, interleukin 6; IL-8, interleukin-8; sTREM2, soluble triggering receptor expressed on myeloid cells 2. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

range, 5). Of the 46 patients, 4 (8.7%) had simple febrile seizure, 24 (52.2%) had complex febrile seizures or fever with convulsion, 5 (10.9%) cases had encephalitis or probable encephalitis, 10 (21.7%) cases had status epilepticus, and 2 (4.3%) had afebrile seizures. Six (13.0%) patients had history of neurodevelopmental disorders or developmental delay (3 GDD, 1 ASD, and 2 speech delay). Their median blood IL-6 level was 31.4 pg/mL; interquartile range, 97 pg/mL. Only one patient reported CSF IL-6 level of 11.8 pg/mL, but the specimen was collected on Day 11 of illness. Eight (17.4%) patients died due to neurological complications.

4 | DISCUSSION

While most children infected with Omicron develop a self-limiting respiratory disease, neurological manifestations have been occasionally reported. However, the clinical spectrum, outcomes, and potential biomarkers are incompletely understood. The present study describes the clinical characteristics of pediatric patients infected with Omicron who presented with various neurological manifestations. Despite the relatively small sample size, our study had provided some important findings. Based on our cohort of fifteen Omicron-infected children who presented with neurological manifestations and the findings from our systematic review,[17,31–37] we have highlighted Omicron as a differential cause of not only severe neurological manifestations in febrile children, but also those who present with benign febrile seizure.

Potential biomarkers associated with disease severity and outcome in pediatric COVID-19 patients with neurological manifestations are understudied. While it has been well recognized that blood IL-6 level may be a marker found in severe COVID-19, the CSF inflammatory marker changes in the majority of pediatric COVID-19 patients with neurological manifestations were unknown. The present study provided preliminary evidence that children with Omicron-related neurological manifestations had higher CSF IL-6 level without detectable SARS-CoV-2 RNA than those with non-COVID-19-related febrile illnesses. Moreover, CHI3L1, a neuroinflammatory marker indicative of activation and damage of astrocytes was also significantly raised. Correlation analysis showed that higher CSF-to-blood IL-8 and CHI3L1 ratios were associated with longer length of hospitalization. Higher CSF-to-blood IL-6 and IL-8 ratios were associated with higher tau in blood suggestive of neuronal damage. These findings suggested that blood IL-6, IL-8, and CHI3L1 levels may be useful indicators of COVID-19–related neurological manifestations. However, the outcomes of children with neuro-COVID and neuronal damage were related to the disproportionately high levels of cytokines or neuroinflammation within the brain rather than related to the magnitude of cytokines or neuroinflammatory markers in the CSF or blood alone. In contrast to data reported among adult COVID-19 patients, the CSF protein level of Omicron-infected children were not significantly increased.[14] This suggests that Omicron may trigger significant inflammation within the brain through activation of intracellular signaling pathways that lead to tissue-specific cytokine release

TABLE 3 Correlation between the clinical characteristics and the markers among pediatric neuro-COVID patients.

	PCPC	Length of stay (days)	No. of seizures	Tau blood	Tau CSF
Ratio IL-6					
r	0.717	0.217	0.437	0.917*	−0.613
N	6	6	4	6	5
FDR-adjusted *p* value	0.217	0.789	0.751	0.020	0.443
Ratio IL-8					
r	0.725	0.889*	−0.065	0.953*	0.115
N	6	6	5	6	5
FDR-adjusted *p* value	0.217	0.035	0.917	0.012	0.443
Ratio sTREM-2					
r	−0.337	0.21	−0.461	−0.527	0.668
N	4	4	4	4	4
FDR-adjusted *p* value	0.663	0.789	0.751	0.473	0.443
Ratio CHI3L1					
r	0.542	0.885*	0.862	−0.335	−0.415
N	7	7	5	7	5
FDR-adjusted *p* value	0.278	0.032	0.240	0.473	0.672

Note: Ratio of markers is expressed in CSF/blood.

Abbreviations: CHI3L1, chitinase-3 like-protein-1; IL-6, interleukin 6; IL-8, interleukin-8; PCPC, Pediatric Cerebral Performance Category; sTREM2, soluble triggering receptor expressed on myeloid cells 2.

*$p < 0.05$ after FDR adjustment.

syndrome.[41] Taken together, our findings suggest that the neurological manifestations in Omicron-infected pediatric patients are more likely due to immunopathology than direct virus-induced damage.

Interestingly, we also found that higher viral load as indicated by lower C_t value was associated with higher CSF level of the microglial activation marker sTREM-2, indicating neuroinflammation in these patients. As COVID-19 vaccines may significantly reduce the viral load of SARS-CoV-2 in infected individuals,[42] our finding highlights the potential benefit of vaccination to reduce the risk of neurological complications. Indeed, we did not identify any fully vaccinated Omicron-infected children who developed neurological manifestations during our study period. Interestingly, one child (Case 4) who had been vaccinated with one dose of the Comirnaty (BioNTech) mRNA vaccine had relatively low level of inflammatory markers in the blood or CSF despite having presented with seizure with fever. Further studies should be conducted to thoroughly investigate the effects of COVID-19 vaccines in the prevention of neurological complications due to COVID-19.

A recent animal study showed that even mild COVID-19 may cause neuroinflammation and multilineage cellular dysregulation in the central nervous system.[43] In this study, we have also shown that higher CSF IL-6 level, CSF-to-blood IL-6 and IL-8 ratios were associated with higher blood level of the neuronal damage marker Tau protein. It is important to note that blood Tau proteins can pass through the blood–brain barrier (BBB) bidirectionally even in the absence of BBB disruption. Therefore, blood-borne tau proteins may potentially contribute to neurodegenerative changes as a result of brain tauopathies in the future.[44] Although the brains of children have much higher neuroplasticity than those of adults, children with history of neuro-COVID should be offered longitudinal follow-up on their neurodevelopment and cognitive function.

Our study had a number of limitations. First, our cohort did not include some children who died of COVID-19 as they were too unstable haemodynamically for recruitment and investigations such as lumbar puncture. However, we have recruited Omicron-infected children with varying disease severity levels (from mild to severe COVID-19 requiring PICU admission). Second, only blood but not CSF specimens were available from the healthy control subjects for neuroinflammatory marker comparison as it was considered too invasive to perform lumbar puncture on the control subjects. Third, our study had a limited sample size. Nevertheless, the present study has identified novel clinical characteristics and potential biomarkers for pediatric patients with Omicron-related neurological complications that should be further investigated in future studies with larger sample size and longitudinal data.

TABLE 4 Characteristics of pediatric patients with COVID-19-related neurological manifestations.

	Age	Gender	Variant	Underlying condition	Presenting symptoms	Neurological manifestation (type)	CSF SARS-CoV-2	CSF (pg/mL)		Blood (pg/mL)		Imaging	EEG	Dead/alive	Length of Hospital Stay
								IL-6	IL-8	IL-6	IL-8				
Wang et al. (2022)	2 years 10 months	F	Omicron		Fever, productive cough, vomiting, decreased appetite and urine output	Encephalitis	Negative	NR	NR	<1.5	NR	Normal CT upon admission T2 MRI (D7): peripheral diffusion restriction in bilateral thalami and pons, with high T1 rim. Edema in bilateral thalami, pons and posterior limb of bilateral internal and external capsule	Excessive slow waves	Alive	10+
Thongsing et al. (2022)	3 months	M	Omicron	–	NR	Complex febrile seizure	NR						Normal	Alive	4
	6 months	F		Febrile convulsion	NR	Complex febrile seizure							–	Alive	0
	14 months	F		–	NR	Complex febrile seizure							–	Alive	0
	14 months	M		Focal epilepsy	NR	Fever with convulsion							–	Alive	1
	17 months	F		–	NR	Complex febrile seizure							Normal	Alive	6
	21 months	M		Febrile convulsion	NR	Benign febrile seizure							–	Alive	0
	23 months	F		–	NR	Complex febrile seizure							–	Alive	2
	2 years	M		Febrile convulsion GDD, autism known MRI subcortical white matter	NR	Complex febrile seizure							–	Alive	0

(Continues)

TABLE 4 (Continued)

Age	Gender	Variant	Underlying condition	Presenting symptoms	Neurological manifestation (type)	CSF SARS-CoV-2	CSF (pg/mL)		Blood (pg/mL)		Imaging	EEG	Dead/alive	Length of Hospital Stay
							IL-6	IL-8	IL-6	IL-8				
			signal abnormality											
2 years	M		Febrile convulsion Hx of HIE	Focal seizure	Complex febrile seizure							Electrical seizures originating from right central region, lasting <30 s each	Alive	6
3 years	F		–	Focal seizure	Status epilepticus							–	Alive	2
4 years	F		Known absence of septum pellucidum, and small optic nerve on MRI	NR	Complex febrile seizure							Background slow disorganized, no focality	Alive	8
6 years	F		Focal epilepsy	NR	Complex febrile seizure							Abundant left posterior quadrant spikes and polyspikes	Alive	5
6 years	M		Focal epilepsy	NR	Complex febrile seizure							–	Alive	1
7 years	M		–	NR	Status epilepticus							–	Alive	3
10 years	F		Focal epilepsy Right hemispheric stroke and venous sinus thrombus	NR	Status epilepticus							–	Alive	0
12 years	M		Focal epilepsy	NR	Breakthrough seizures							–	Alive	0

TABLE 4 (Continued)

	Age	Gender	Variant	Underlying condition	Presenting symptoms	Neurological manifestation (type)	CSF SARS-CoV-2	CSF (pg/mL)		Blood (pg/mL)		Imaging	EEG	Dead/alive	Length of Hospital Stay
								IL-6	IL-8	IL-6	IL-8				
Ludvigsson (2022)	3 months	M	NR	–	Convulsion and fever	Complex febrile seizure	Negative	NR	NR	NR	NR	Normal CT Normal MRI	No epileptiform activity	Alive	4
	21 months	M	NR	–	GTC and fever	Status epilepticus	–	NR	NR	NR	NR	–	–	Alive	2
	14 years	M	NR	Recurrent UTI	GTC, postictal behavioral changes sore throat. No fever	Afebrile seizure	–	NR	NR	NR	NR	–	–	Alive	2
Tetsuhara et al. (2022)	29 days	M	BA.1	–	Pallor, apnea with bradycardia. Afebrile. Non-convulsive status epilepticus Myoclonic movement in lower limbs with conjugate eye deviation to left	Probable encephalitis	Negative	11.8 (D11)	–	46.7 (D5) <1.5 (D29)	–	D14: MRI T2 hyperintensity and FLAIR hypointensity in deep and subcortical white matter of left frontal, bilateral temporal and parietal lobes. Hyperintensity on DWI in corpus callosum D45: multiple cystic cavitations in left cerebral hemisphere, right temporal, occipital and parietal lobes. Left epidural fluid accumulation. Basal ganglia and thalamus are intact	D4: rhythmic spike or spike and wave complex of 1.5–2 Hz occurred mostly in the left hemisphere for several minutes at frequent intervals D7: ictal pattern during myoclonic movement	Alive	13d in ICU Home on D30

(Continues)

TABLE 4 (Continued)

	Age	Gender	Variant	Underlying condition	Presenting symptoms	Neurological manifestation (type)	CSF SARS-CoV-2	CSF (pg/mL)		Blood (pg/mL)		Imaging	EEG	Dead/alive	Length of Hospital Stay
								IL-6	IL-8	IL-6	IL-8				
Ilio et al. (2022)	7 years	F	BA.1	–	GTC, fever	Fever with convulsion	Not done					–	–	Alive	NR
	8 years	F	BA.1	Febrile convulsion	Tonic seizure, fever	Fever with convulsion						–	–	Alive	NR
	6 years	M	BA.1	Febrile convulsion	Tonic seizure, fever	Fever with convulsion						–	–	Alive	NR
	9 years	M	BA.1	Severe mitral stenosis, MV replacement, sick sinus syndrome, periventricular leukomalacia	Status epilepticus, fever	Status epilepticus						CT: No cerebral edema. Old ischemic stroke pattern (cystic encephaloma-lacia on right parietal lobe).	intermittent spikes and waves were observed in Fp2. diffuse, high-voltage, slow-wave, electrical storm, or absence of spindle waves were not observed.	Alive	NR
	10 years	F	BA.1	Fever with convulsion	Clonic seizure, no fever	Afebrile seizure						–	–	Alive	NR
Kinikar et al. (2022)	18 months	M	BA.1	Anemia, moderate acute malnutrition	GTC, fever	Simple febrile seizure	NR	NR	NR	19	NR	NR	NR	Alive	6
	4 months	F	BA.1	–	Fever, seizure	Encephalopathy	NR	NR	NR	4	NR	NR	NR	Dead	31
	10 years	M	BA.2	Epilepsy	GTC, fever	Fever with convulsion	NR	NR	NR	35	NR	NR	NR	Alive	6
	6 years	M	BA.2	Epilepsy Klebsiella pneumonia sepsis	GTC, fever, cough	Fever with convulsion	NR	NR	NR	14.14	NR	NR	NR	Alive	14

TABLE 4 (Continued)

	Age	Gender	Variant	Underlying condition	Presenting symptoms	Neurological manifestation (type)	CSF SARS-CoV-2	CSF (pg/mL)		Blood (pg/mL)		Imaging	EEG	Dead/alive	Length of Hospital Stay
								IL-6	IL-8	IL-6	IL-8				
	3 years	M	BA.2	Epilepsy	Status epilepticus, fever	Status epilepticus	NR	NR	–	NR	NR	NR	NR	Dead	1
	3 months	F	BA.2	Intracranial bleed, dural venous sinus thrombosis	GTC, fever, cough	Fever with convulsion	NR	NR	–	111.9	NR	NR	NR	Alive	14
Chen et al. (2022)	5 years	F	BA.2.3.7	NR	GTC Fever, drowsiness, nonsensical babbling Shock complicated with multiorgan failure	Fever with convulsion	NR	NR	NR	1111	NR	NR	NR	Alive	NR
	4 years	F	BA.2.3.7	NR	GTC, fever, drowsiness	Fever with convulsion	Negative	NR	NR	31.4	NR	NR	NR	Alive	NR
	1 years	M	BA.2.3.7	NR	Convulsion, fever, vomiting, dizziness	Fever with convulsion	Negative	NR	NR	6.5	NR	NR	NR	Alive	NR
	3 years	F	BA.2.3.7	NR	Convulsion, fever, abdominal pain, vomiting	Fever with convulsion	NR	NR	NR	6.8	NR	NR	NR	Alive	NR
	2 years 5 months	M	BA.2.3.7	NR	Convulsion, fever, bilateral upward gaze with loss of consciousness and cyanosis of lips	Fever with convulsion	Negative	NR	NR	103.3	NR	NR	NR	Alive	NR

(Continues)

TABLE 4 (Continued)

	Age	Gender	Variant	Underlying condition	Presenting symptoms	Neurological manifestation (type)	CSF SARS-CoV-2	CSF (pg/mL)		Blood (pg/mL)		Imaging	EEG	Dead/alive	Length of Hospital Stay
								IL-6	IL-8	IL-6	IL-8				
Lin et al. (2022)	3 years 2 months	M	BA.2		Altered mental status, tonic seizures	Fulminant cerebral edema	Negative	NR	NR	NR	NR	Brain CT: Acute necrotizing encephalopathy uncal herniation	NR	Dead	
	2 years 4 months	M	BA.2		Altered mental status, focal seizure	Status epilepticus Fulminant cerebral edema	NR	NR	NR	NR	NR	Brain CT: Brainstem hypodensity ncal herniation	NR	Dead	
	2 years	M	BA.2		GTC no return of consciousness	Sulminant cerebral edema	NR	NR	NR	NR	NR	NR	NR	Dead	
	4 years	F	BA.2		Behavior change, visual hallucination, GTC	Status epilepticus fulminant cerebral edema	NR	NR	NR	NR	NR	Brain CT: Decreased size of the suprasellar cistern, uncal herniation	NR	Dead	
	10 years 2 months	M	BA.2		Dizziness, visual hallucination, tonic seizure	Status epilepticus fulminant cerebral edema	Negative	NR	NR	NR	NR	Brain CT: 1st: mild cerebral edema 2nd: uncal herniation	NR	Dead	
	4 years	F	BA.2		Altered mental status, GTC	Status epilepticus fulminant cerebral edema	NR	NR	NR	NR	NR	Brain CT: Cerebral edema with impeding uncal herniation	NR	Dead	
Cautilli et al. (2023)	12	M	Omicron			Acute disseminated encephalomyelitis	Negative	Negative	Negative	Negative	Negative	MRI showed signs of transverse myelitis	normal	Alive	NR
Sano et al. (2023)	9	M	Omicron	A history of cryptorchidopexy and mild left renal pelvis dilation	Vomiting and generalized seizure	Encephalopathy	NR	NR	NR	NR	NR	Brain CT showed low density areas that predominantly affected the	NR	Alive	

TABLE 4 (Continued)

	Age	Gender	Variant	Underlying condition	Presenting symptoms	Neurological manifestation (type)	CSF SARS-CoV-2	CSF (pg/mL)		Blood (pg/mL)		Imaging	EEG	Dead/alive	Length of Hospital Stay
								IL-6	IL-8	IL-6	IL-8				
												posterior bilateral regions			
Cheng et al. (2023)	6	M	BA.2.3		Febrile convulsion	Acute encephalitis	NR	NR	NR	100.6	NR	CT scan revealed tight ventricles without mass lesions and a left lower lung consolidation patch	NR	Alive	

Abbreviations: F, female; GTC, generalized tonic-clonic seizure; M, male; NR, not reported.

AUTHOR CONTRIBUTIONS

Winnie Wan-Yee Tso, Patrick Ip, and Jasper Fuk-Woo Chan contributed to conceptualization, funding acquisition, supervision, and writing—original draft, reviewing and editing. Mike Yat-Wah Kwan, Janette Siu-Yin Kwok, Jessica Oi-Ling Tsang, Cyril Chik-Yan Yip, Lok-Kan Leung, Cuixin Li, Yuliang Wang, Mathew Siu-Chun Chow, Anita Man-Ching Tsang, Stella Chim, Chin-Ying Chow, Alvin Chi-Chung Ho, Sophelia Hoi-Shan Chan, Shuk-Mui Tai, Wing-Cheong Lee, Victor Chi-Man Chan, Eric Kin-Cheong Yau, Jacquelyne Ka-Li Sun, Hei-Man Chow, and Yu-Lung Lau contributed to investigation, data curation, and/or writing—reviewing and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. All data generated or analyzed during this study are included in the article. The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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