



Acute encephalopathy in unvaccinated children infected with the Omicron variant of SARS-CoV-2 (Japanese nationwide epidemiological study) | 1

Acute encephalopathy (AE) is the most serious complication of common infectious diseases. The primary manifestation of AE in pediatric patients during an infectious disease is the acute onset of severe and long-lasting impairment of consciousness. The AE is a heterogeneous condition that often leads to death or severe neurological sequelae. The pathological substrate is a noninflammatory brain edema, diffuse or widespread in distribution, and vascular or cellular in nature. Neuroimaging techniques like cranial computed tomography (CT) or magnetic resonance imaging (MRI) are robust tools for visualizing brain edema. (M. Mizuguchi et al. *Brain & Development* 2021; 43: 2-31.) [https://www.brainanddevelopment.com/article/S0387-7604\(20\)30215-1/fulltext](https://www.brainanddevelopment.com/article/S0387-7604(20)30215-1/fulltext) The Japanese authors conducted a nationwide epidemiological study to investigate epidemiological differences in acute encephalopathy in children infected with the Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). They compared the results from the period in which BA.5 or BA.1/BA.2 prevailed. They also investigated the epidemiological differences between AE associated with SARS-CoV-2 infection and AE not associated with SARS-CoV-2 infection.

The authors noted that the number of pediatric patients requiring hospitalization in Japan increased during Omicron variants compared to the pre-Omicron period. One previous study demonstrated a higher rate of febrile seizures and unconsciousness associated with the Omicron variant infection in children compared to non-Omicron variants. <https://discovermednews.com/omicron-variant-is-more-likely-to-cause-febrile-seizures-and-unconsciousness-in-children/>

About the study

The study included Japanese pediatric patients, younger than 18 years, who developed AE when the Omicron variants were prevalent in Japan. The cases with the onset when BA.5 prevailed were compared with those from the period when BA.1/BA.2 prevailed. The BA.1, BA.2, and BA.5 subvariants were determined by the periods when each subvariant prevailed, and not by phylogenetic analysis of SARS-CoV-2. In addition, the authors used data from 2014–2017 to investigate the epidemiological differences in clinical and radiological manifestations between AE not associated with SARS-CoV-2 infection and AE associated with SARS-CoV-2 infection. The following data about participants were included: age, gender, clinical diagnosis of AE, history of COVID-19 vaccination, presence of underlying diseases, neurological examination, and complications.

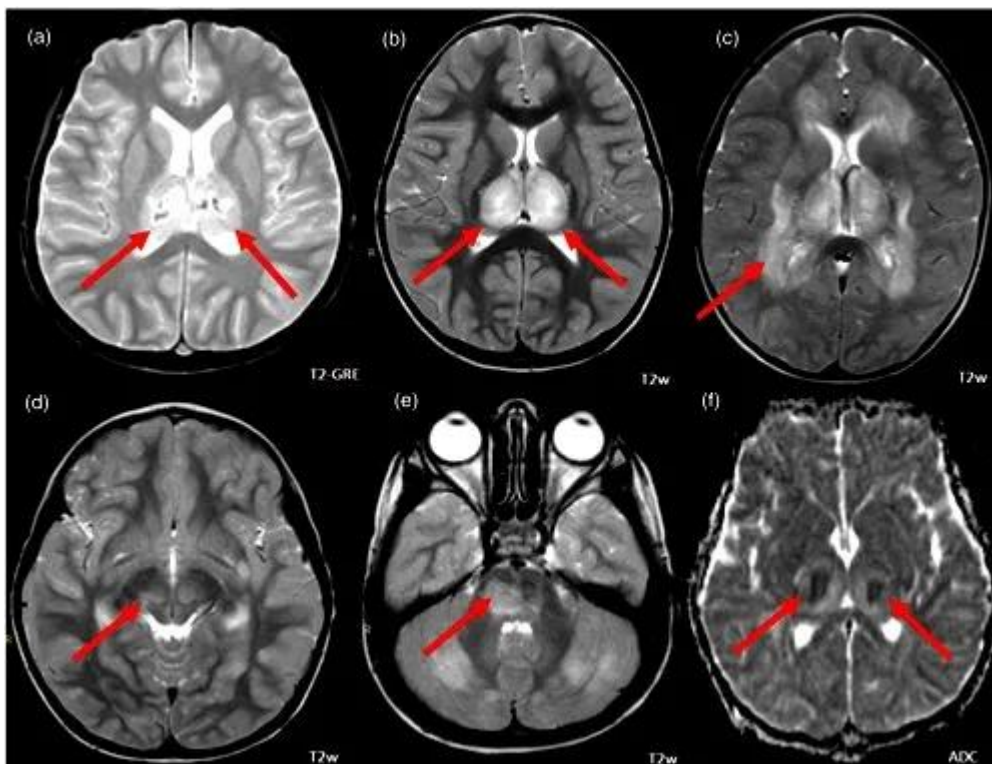
The criteria for AE associated with Omicron SARS-CoV-2 infection were as follows: 1) the

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acute onset of impaired consciousness (Glasgow Coma Scale <11) or altered state of consciousness (abnormal behavior or personality) lasting for 24 hours or longer, 2) the acute onset of the neurological symptoms within two weeks of the diagnosis of COVID-19 or multisystemic inflammatory syndrome in children associated with COVID-19, 3) the evidence of infection with SARS-CoV-2 (reverse transcription polymerase chain reaction for SARS-CoV-2, antigen test, antibody test, and another sample testing), and 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 were categorized into six syndromes according to clinical and radiological manifestations: 1. AE with biphasic seizures and late reduced diffusion, 2. AE with acute fulminant cerebral edema, 3. acute necrotizing encephalopathy, 4. febrile infection-related epilepsy syndrome, 5. hemorrhagic shock and encephalopathy syndrome, and 6. clinically mild encephalitis/encephalopathy with a reversible splenic lesion.



Original illustration from the study of Kasai M, Sakuma H, Abe Y, et al. 2024



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Results

The study included 103 cases of AE associated with SARS-CoV-2 infection, registered during the outbreak of the Omicron variants. Among these, 68 patients met the criteria when BA.5 prevailed, whereas 32 patients met the criteria when BA.1/BA.2 prevailed.

The median age of pediatric patients with AE was 3 years (ranging from 0 to 15 years) and the male-to-female ratio was 1.6: 1.

Among the 103 patients who developed AE associated with SARS-CoV-2, 95 (92.2%) had not been vaccinated against SARS-CoV-2. Out of the 68 patients who met the criteria for AE when BA.5 prevailed, 61 had not been vaccinated against SARS-CoV-2, three were vaccinated and four cases had no data.

There was no significant difference in the incidence of AE between the periods in which BA.1/BA.2 or BA.5 prevailed. In more than 90% of pediatric cases infected with Omicron variants, the first symptoms of AE were seizures, impaired consciousness, and abnormal speech and behavior. The BA.5 subvariant was associated with a higher risk of seizures. The percentage of patients who developed seizures as the first neurological symptom increased by 23.5% during the period when BA.5 was prevalent.

During the BA.5 period, 37% (25 patients) with AE recovered and returned to baseline, 50% (34 patients) experienced a neurological disability and 10% (7 patients) died.

A higher number of patients diagnosed with AE associated with SARS-CoV-2 infection experienced severe disability or even death than patients with non-SARS-CoV-2-associated AE (from 2014-2017). Among the six syndromes studied, two severe syndromes that frequently lead to neurologic disability or death, AE with acute fulminant cerebral edema and hemorrhagic shock and encephalopathy syndrome, were more frequent in SARS-CoV-2 associated AE than in non-SARS-CoV-2 associated AE. All patients diagnosed with these syndromes had not been vaccinated against SARS-CoV-2.

Conclusion

This study demonstrated a similar clinical presentation of acute encephalopathy associated



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with SARS-CoV-2 in pediatric patients during the BA.1/BA.2 or BA5 predominant periods, except for a higher risk of seizures during the period when BA.5 was predominant.

Importantly, a significantly higher number of patients with SARS-CoV-2-associated AE experienced severe disability or even death than patients with AE not associated with SARS-CoV-2.

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Journal Reference

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