Acute necrotizing encephalopathy is a rare form of acute encephalopathy that mostly affects children, and is characterized by an altered state of consciousness, usually accompanied by seizures. It was first described in 1995 by Mizuguchi et al. (Mizuguchi M, Abe J, Mikkaichi K, et al. Acute necrotizing encephalopathy of childhood: a new syndrome presenting with multifocal, symmetric brain lesions. J Neurol Neurosurg Psychiatry 1995; 58: 555-561). In this single-center retrospective study, the authors from China investigated the clinicopathogenic characteristics of infection with the Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a large cohort of 4,520 pediatric patients.

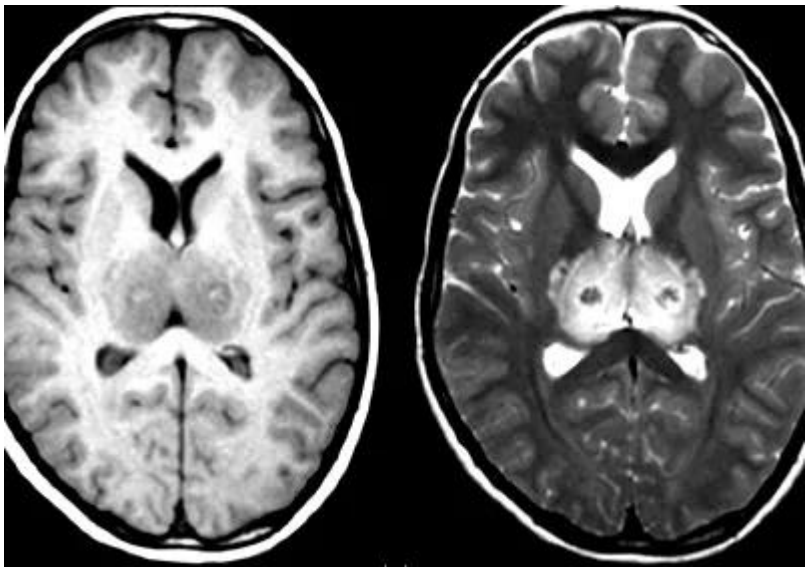
Mizuguchi et al. proposed the following diagnostic criteria: encephalitis preceded by viral infections, altered consciousness, no pleocytosis in cerebrospinal fluid analysis, elevated aminotransferase levels, exclusion of other diseases with similar clinical symptoms, and finally, radiologic features. These radiologic findings, characteristic of acute necrotizing encephalopathy, consist of symmetrical bilateral brain lesions affecting the thalami, upper tegmentum, putamen, periventricular white matter, and cerebellum. A poorer outcome was observed in patients with a higher degree of thalamic involvement.

The pathophysiology of acute necrotizing encephalopathy is not completely understood. According to some theories, acute necrotizing encephalopathy is an immune-mediated disease triggered by viral infections such as influenza A and B, parainfluenza, human herpes virus-6, or dengue. Hypercytokinemia, also known as “cytokine storm,” is the most widely accepted theory, characterized by elevated serum levels of interleukin (IL)-6, -10, -15, and -1β; tumor necrosis factor-α (TNF-α); and interferon-γ. The histopathology examinations of brain tissue showed coagulative necrosis and microhemorrhages around the small vessels in the involved brain regions, but lymphocytic and neutrophilic infiltrates were not observed. A lack of cellular inflammatory response suggests a distant effect secondary to the primary inciting event, commonly a viral infection. H.A. Vanjare et al. Clinical and radiologic findings of acute necrotizing encephalopathy in young adults. Am Journal Neuroradiol 2020, 41 (12) 2250-2254. https://doi.org/10.3174/ajnr.A6803

A recent Japanese nationwide epidemiological study investigated the epidemiological differences of six syndromes of acute encephalopathy in children infected with the Omicron variant of SARS-CoV-2, including acute necrotizing encephalopathy. The findings revealed that a higher number of patients with acute encephalopathy associated with SARS-CoV-2 experienced severe disability or even death than patients diagnosed with acute encephalopathy which was not associated with SARS-CoV-2. In more than 90% of pediatric cases infected with Omicron variants, the first symptoms of acute encephalopathy were

seizures, impaired consciousness, and abnormal speech and behavior. https://discovermednews.com/acute-encephalopathy-associated-with-sars-cov-2-infection-in-children-during-the-omicron-period/

In addition, children infected with the Omicron variant of SARS-CoV-2 have a high incidence of febrile seizures, but the underlying pathogenic mechanism is not elucidated. https://discovermednews.com/omicron-variant-is-more-likely-to-cause-febrile-seizures-and-unconsciousness-in-children/



About the study

This retrospective, observational, single-center study was conducted on pediatric patients infected with the Omicron variant and admitted to The Affiliated Children's Hospital of Xi'an Jiaotong University in Xi'an, China. COVID-19 was confirmed by positive reverse transcription polymerase chain reaction of nasopharyngeal swabs for SARS-CoV-2, and the Omicron variant was confirmed by whole-genome sequencing.

Data were extracted from the electronic medical records and included diagnosis, clinical signs, symptoms, treatment, and laboratory data, such as blood cell count, hypersensitive C-reactive protein (hs-CRP), and liver and myocardial enzyme concentrations.

Results

The study included 4,520 pediatric patients infected with the Omicron variant of SARS-CoV-2, categorized into two groups: an inpatient group of 659 patients (15%) and an outpatient group of 3,861 patients (85%). 58% of them were males and 42% were females. The age ranged from newborns to 18 years, however, the majority of children were between 1 and 3 years old. The median age was 2 years.

In the group of 3,861 outpatients, the main diagnosis was upper respiratory tract infection (URTI), diagnosed in 88% of the patients. 10% of the patients had bronchitis, and 2% had pneumonia. The most frequent clinical presentation in outpatients were convulsions, observed in 37% of the patients, followed by laryngitis in 22%, vomiting in 21%, abdominal pain in 5%, diarrhea in 4%, rash in 2%, enlarged tonsils in 4%, thrombocytopenic purpura in 1%, acute gastroenteritis in 1%, allergic reaction in 0.2%, and sepsis in 0.2%.

The hospitalized group included 659 patients. 26% of patients were diagnosed with URTI, 15% with bronchitis, and 36% with pneumonia. Importantly, a significant number of patients within this group were diagnosed with severe neurological diagnoses, including 18 patients with viral encephalitis, 7 with toxic encephalopathy, 5 with acute necrotizing encephalopathy, 1 with cerebral infarction, 1 with cerebrospinal meningitis, and 18 with seizures. Other serious diagnoses included sepsis (13 patients), fulminant myocarditis (1 patient), vomiting and diarrhea (9 patients), gastrointestinal bleeding (2 patients), allergic purpura (2 patients), immune thrombocytopenia (10 patients), nephritis (10 patients), diabetes (2 patients), appendicitis (11 patients) and Kawasaki disease (5 patients).

Febrile seizures occurred in 49% of patients with URTI, 35% of patients with bronchitis, and 5% of patients with pneumonia. Myocardial damage also occurred mainly in patients with URTI (6%), bronchitis (12%), and pneumonia (8%). The finding of convulsions as the most frequent clinical presentation in the outpatient group, and the occurrence of febrile seizures in nearly 50% of hospitalized patients with URTI are consistent with previous works which have shown that the Omicron variant of SARS-CoV-2 is more likely to cause seizures and unconsciousness in pediatric patients compared to the non-Omicron variants.

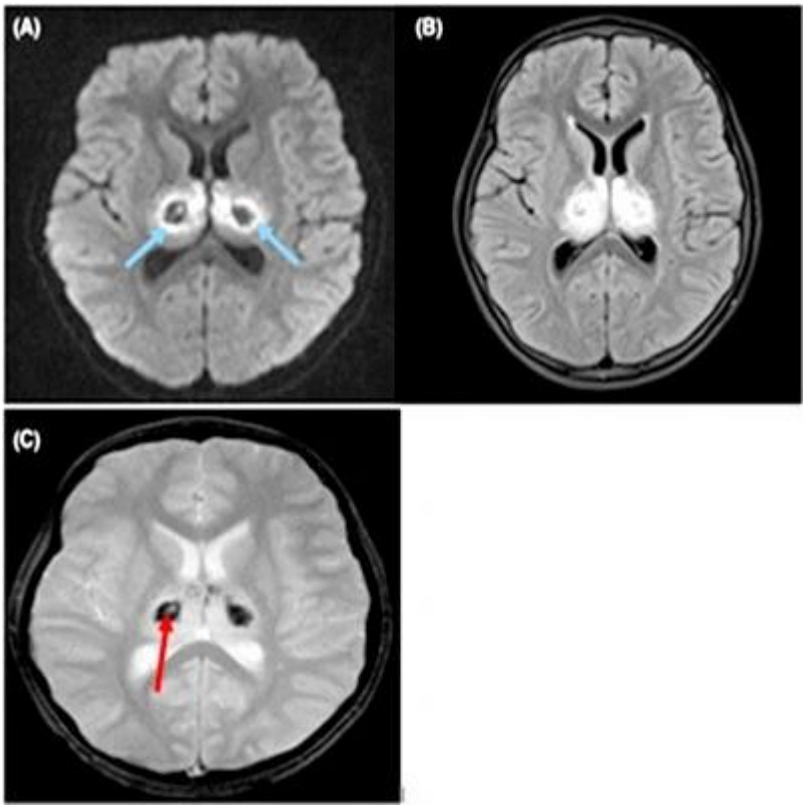
In the inpatient group, laboratory tests revealed that alanine aminotransferase (ALT) was elevated in 18% of patients (118 inpatients), aspartate aminotransferase (AST) in 49% (323 patients), creatine kinase isoenzyme in 46% (305 patients) and procalcitonin in 25% (167

patients).

Nine patients died. Five of them were diagnosed with acute necrotizing encephalopathy, and presented with high fever or extremely high fever, convulsions, and coma. Two cases had congenital malformations, hypoplastic cerebellum, and intestinal duplication, and three cases had bronchopneumonia. Five patients who died were males and four were females. The median age was 1.92 years (from 0.41 to 14.58 years). In the group of nine patients who died, the procalcitonin serum level was elevated in six patients, blood lactic acid in five patients, creatine kinase isoenzyme in five patients, ALT in four patients, and AST in seven patients.

In all patients who died from acute necrotizing encephalopathy, brain magnetic resonance imaging showed bilateral thalamic symmetrical damage, which is characteristic of acute necrotizing encephalopathy, and other lesions localized in the brainstem, cerebellum, the parietal cortex, periventricular white matter, corpus callosum, basal ganglia, external and internal capsule, centrum semiovale, temporal lobe, and amygdala. All patients had bilaterally symmetrical lesions, frequently with cytotoxic edema, ischemia, and necrotizing changes in the lesion area.

Spearman’s correlation analysis between laboratory findings and clinical diagnoses revealed that AST was positively correlated with the frequency of convulsions, whereas ALT and procalcitonin were negatively correlated with acute necrotizing encephalopathy and death.



The original image from the article of Yue J et al. Front. Pediatr. 2024; 12: 1325562.

Conclusion

This retrospective study of 4,520 pediatric patients infected with the Omicron variant of SARS-CoV-2 demonstrated that acute necrotizing encephalopathy and pneumonia with comorbidities were the main causes of death.

The authors noted that the mortality rate of hospitalized children in this study was 1.37% (9/659), much lower than the adult mortality rate (4.3%), but, the most common causes of death in adults were acute respiratory distress syndrome, severe viral pneumonia, and multiple organ failure, rather than severe neurological diagnoses, such as encephalitis. The researchers recommended that clinicians should have a high suspicion for acute necrotizing encephalopathy in the pediatric age group when there is high or very-high fever, progressively impaired consciousness, neurological deficits, and a history of viral infections, particularly upper respiratory tract infections.

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Journal Reference

Yue J, Cao J, Liu L, et al. Clinical characteristics of 4,520 pediatric patients infected with the SARS-CoV-2 omicron variant, in Xi'an, China. Front. Pediatr. 2024; 12: 1325562. https://doi.org/10.3389/fped.2024.1325562