Article published online: 2024-09-25

Radiological Insights into Acute Leukoencephalopathy with Restricted Diffusion (ALERD): A Case Series Analysis

Satwik Jayaramu[1] Diwakar Doddamani[1]

[1] Department of Radiodiagnosis, J. J. M. Medical College and Hospital, Davanagere, Karnataka, India

Indian J Radiol Imaging

Address for correspondence Satwik Jayaramu, MBBS, MD, Department of Radiodiagnosis, J. J. M. Medical College and Hospital, Davanagere, Karnataka 577004, India (e-mail: satwik1296@gmail.com).

Abstract

Objectives The study aimed to investigate the clinical and radiological characteristics of acute leukoencephalopathy with restricted diffusion (ALERD) among pediatric patients presenting with acute encephalopathy, seizures, and fever.

Methods A retrospective analysis was conducted on 48 pediatric patients who underwent magnetic resonance imaging (MRI) between April 2022 and August 2023 at Bapuji Hospital, J.J.M. Medical College, Davanagere, Karnataka, India. Inclusion criteria comprised acute-onset encephalopathy, fever, seizures, and MRI evidence of acute subcortical white matter involvement. Clinical and radiological data were collected and analyzed to delineate ALERD characteristics.

Results Among the study cohort, 18.7% of cases met the diagnostic criteria for ALERD, predominantly affecting male children with a mean age of 32 months. Clinical presentations varied, including biphasic and monophasic courses. Two distinct patterns of brain involvement, diffuse and central-sparing, were identified. Laboratory abnormalities and differential diagnoses were elucidated, providing insights into distinguishing ALERD from other conditions. MRI, particularly diffusion-weighted imaging, emerged as a crucial tool for ALERD diagnosis, revealing characteristic restricted diffusion patterns.

Conclusion The study underscores the importance of recognizing ALERD as a distinct clinical-radiological syndrome associated with infections, aiding in timely diagnosis and management. Understanding the varied clinical presentations and radiological patterns enhances diagnostic accuracy, emphasizing the role of MRI in ALERD diagnosis. These findings contribute to a comprehensive understanding of ALERD, facilitating improved patient outcomes and prognosis.

Keywords

- acute leukoencephalopathy with restricted diffusion (ALERD)
- diffusion-weighted imaging (DWI)
- apparent diffusion coefficient (ADC)
- acute encephalopathy
- acute encephalopathy with biphasic seizures and late reduced diffusion (AESD)

Introduction

Acute encephalopathy represents a critical neurological condition characterized by a sudden onset of symptoms such as seizures, altered consciousness, and various neurological deficits. Predominantly affecting young children, this condition often arises as a complication of viral infections and can lead to significant morbidity and mortality. Accurate and timely diagnosis is crucial for effective treatment and prognosis. Common etiologies include febrile encephalopathies (like viral

DOI https://doi.org/10.1055/s-0044-1791231.
ISSN 0971-3026.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

meningoencephalitis and bacterial meningitis), systemic disorders (such as dyselectrolytemia, hepatic or renal failure, and sepsis), hypoxic-ischemic events, toxins, traumatic brain injury, and stroke.[1]

In recent years, a new entity known as acute leukoencephalopathy with restricted diffusion (ALERD) has emerged, particularly in East Asia.[2] ALERD, often associated with infections, presents with fever and prolonged seizures, and although it has a lower mortality rate, it frequently results in neurological sequelae.[3] ALERD can manifest in two forms: diffuse ALERD, which involves severe clinical features and rapid deterioration, and central-sparing ALERD, which presents a milder clinical picture with a characteristic biphasic course. This biphasic course often starts with a prolonged febrile seizure followed by initial improvement, but can lead to delayed cognitive impairment, underlining the importance of recognizing and differentiating these subtypes for appropriate management.[1–4] This study explores ALERD's clinical and radiological features, emphasizing magnetic resonance imaging (MRI) findings and diagnostic challenges, through comprehensive case series analysis.

Materials and Methods

A retrospective study was conducted at the Department of Radiodiagnosis, Bapuji Hospital, J.J.M. Medical College, Davanagere, Karnataka, India, focusing on patients with acute encephalopathy, specifically those diagnosed with ALERD. The study included 48 patients who underwent MRI using a "Philips 1.5T MRI machine" between April 2022 and August 2023. The analysis centered on cases of acute-onset, nontraumatic encephalopathy, with or without seizures.

Acute encephalopathy was defined by decreased consciousness with or without other neurological symptoms lasting $\geq$ 24 hours in children with infectious symptoms such as fever, cough, and diarrhea. Inclusion criteria comprised children presenting with fever and encephalopathy, with or without seizures, and MRI evidence of acute subcortical white matter involvement. Exclusion criteria included recent hypoxic events, substance intoxication, and traumatic brain injury.

MRI was performed on all 48 patients, with diffusion-weighted images (DWIs) obtained for each patient. Nine patients exhibited widespread diffusion restriction in the cortex and/or subcortical white matter of the bilateral hemispheres and were included in this study. Two distinct patterns of brain lesions were identified in DWI: diffuse lesions and central-sparing lesions.

Laboratory data were assessed from medical records, including platelet counts; alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase, creatinine kinase, blood urea nitrogen, creatinine, glucose, and ammonia levels; and cerebrospinal fluid (CSF) cell counts and protein. This investigation at Bapuji Child Health Institute provides valuable insights into ALERD's clinical and radiological characteristics within a broader encephalopathy cohort. Here, we discuss three representative cases of the nine patients.

Representative Cases

Case 1

A 12-month-old male presented with fever, vomiting, seizures, and altered sensorium following empirical antibiotic treatment. Tachycardia and mild hypotension were observed without signs of dehydration. Neurological examination revealed decreased muscle tone with no meningeal signs. Laboratory tests showed an elevated leukocyte count of 21,478 cells/cu. mm. Malaria and viral infection markers were negative. Normal CSF analyses were reported. Additionally, the presentation was monophasic with shock, acute kidney injury indicated by elevated creatinine of 2.1 mg/dL and blood urea nitrogen of 67 mg/dL, and acute liver failure (ALF) with elevated ALP of 439 U/L, AST of 338 U/L, and ALT of 289 U/L. Inflammatory interleukins (ILs)/cytokine levels were not assessed. MRI of the brain showed bilateral symmetrical areas of subtle T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities with true diffusion restriction in the subcortical and deep white matter of the bilateral cerebral hemispheres, as well as the midbrain and pons, giving a "bright tree appearance" suggestive of a diffuse type of ALERD (►**Fig. 1**).

Case 2

A 48-month-old female child presented with relapsing fever in a remitting pattern and prolonged febrile seizure, followed by initial improvement but later worsened to have cognitive impairment. The presentation was biphasic with shock and ALF, indicated by elevated ALP of 267 U/L, AST of 304 U/L, and ALT of 263 U/L. Laboratory tests revealed an elevated total leukocyte count (TLC) of 19,342 cells/cu.mm and positive dengue markers (NS1 antigen and immunoglobulin M positive), while CSF analysis was normal. Inflammatory ILs/cytokine levels were not assessed. MRI of the brain showed extensive areas of diffusion restriction in the subcortical and deep white matter of the bilateral cerebral hemispheres, with sparing of the primary sensory motor cortex, indicating central-sparing ALERD (►**Fig. 2**).

Case 3

A 20-month-old male presented with fever, seizures, and altered sensorium. The presentation was monophasic and accompanied by shock. Laboratory findings revealed an elevated TLC of 23,186 cells/cu.mm. Viral markers were negative, and CSF analysis was normal. Inflammatory ILs/cytokine levels were not assessed. MRI of the brain showed bilateral symmetrical areas of subtle T2/FLAIR hyperintensities with true diffusion restriction in the subcortical and deep white matter of the bilateral cerebral hemispheres. This pattern gave rise to a "bright tree appearance," indicating a diffuse type of ALERD (►**Fig. 3**).

Discussion

ALERD represents a distinct clinical-radiological entity within the spectrum of acute encephalopathy, particularly in pediatric populations. This retrospective study at the

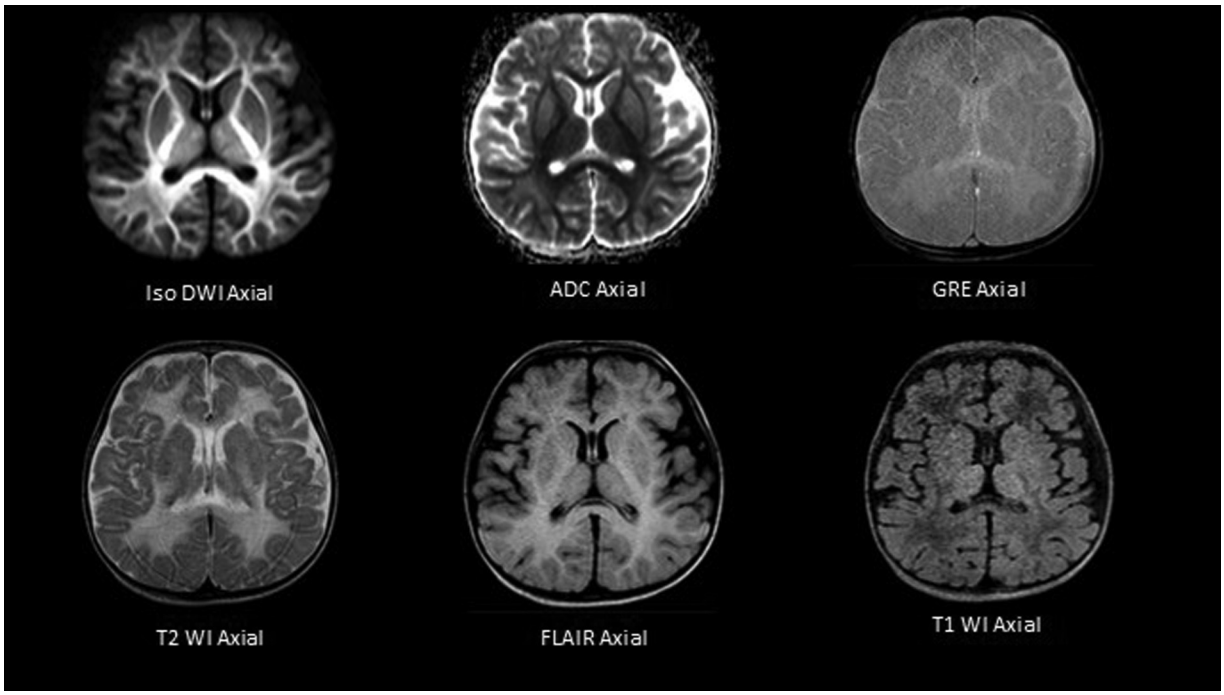

Fig. 1 Bilateral symmetrical areas of subtle T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities showing true diffusion restriction in subcortical and deep white matter of bilateral cerebral hemispheres as well as midbrain and pons, giving "bright tree appearance"—diffuse type of acute leukoencephalopathy with restricted diffusion.

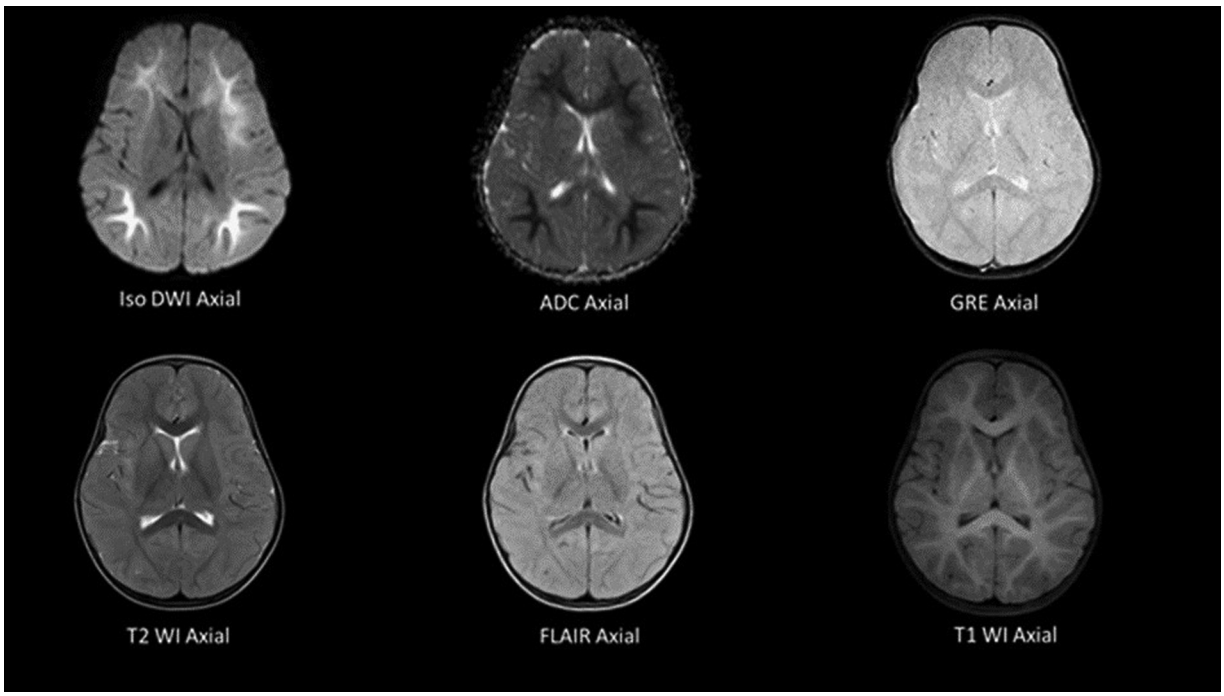

Fig. 2 Extensive areas of diffusion restriction in subcortical and deep white matter of bilateral cerebral hemispheres with sparing of the primary sensory motor cortex. Central-sparing acute leukoencephalopathy with restricted diffusion.

Department of Radiodiagnosis in Bapuji Hospital, J.J.M. Medical College, has provided valuable insights into the clinical and radiological characteristics of ALERD, contributing to a comprehensive understanding of this condition. Out of 48 cases of acute-onset nontraumatic encephalopathy, 9 children (18.7%) met the diagnostic criteria for ALERD. The study group exhibited a male preponderance (5 out of 9) with a mean age of 32 months (range: 6–60 months) at presentation (►**Table 1**). The clinical presentation of ALERD is characterized by acute encephalopathy with fever, often accompanied by altered consciousness and prolonged seizures lasting more than 30 minutes. Seizures can be generalized, partial,

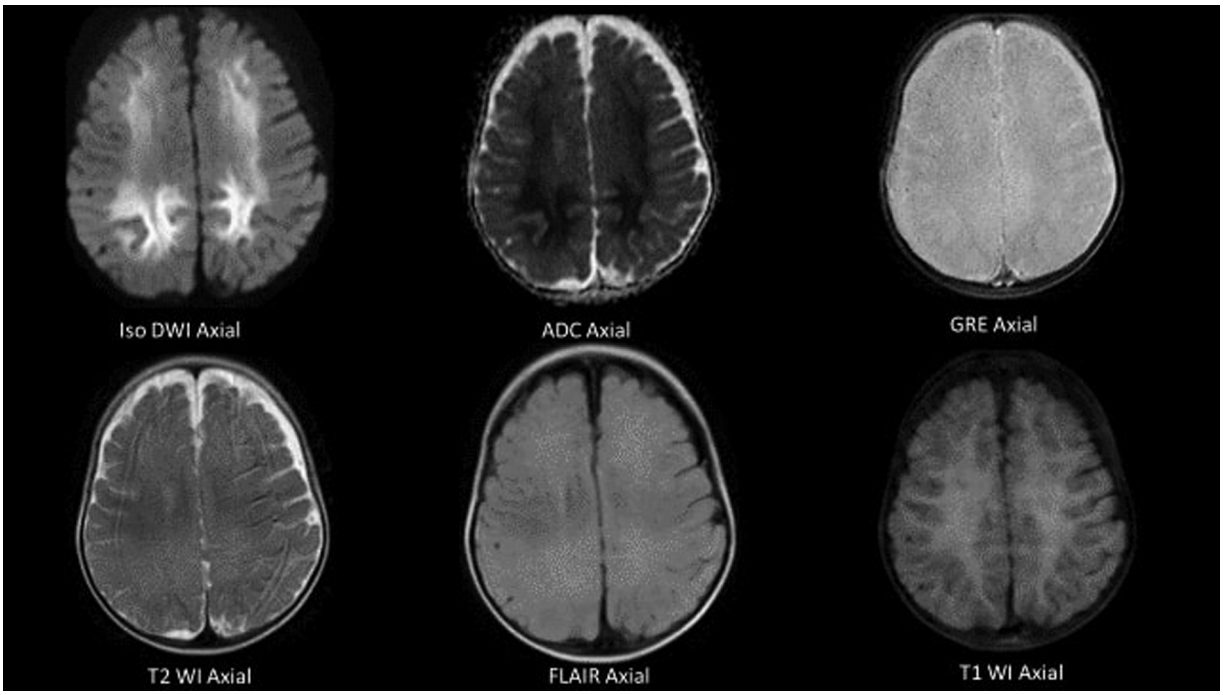

Fig. 3 Bilateral symmetrical areas of subtle T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities showing true diffusion restriction in subcortical and deep white matter of bilateral cerebral hemispheres, giving "bright tree appearance"—diffuse type of acute leukoencephalopathy with restricted diffusion.

recurrent, or nonconvulsive.[2] Notably, three children exhibited a biphasic course, including two with typical acute encephalopathy with biphasic seizures and late reduced diffusion, while six displayed a monophasic course. These clinical patterns underline the variability in ALERD presentations, ranging from severe to relatively mild forms.

The pathogenesis of ALERD involves hypercytokinemia, as evidenced by elevated levels of IL-6, IL-8, IL-10, and tumor necrosis factor in the serum and CSF. Excitotoxic neuronal injury with delayed or apoptotic neuronal death may contribute to ALERD pathogenesis, and some cases are associated with hemophagocytic syndrome, suggesting a role for hypercytokinemia in its development.[5] Laboratory abnormalities in ALERD may include increased liver enzymes, hyperglycemia, hypercytokinemia, and metabolic acidosis, particularly in cases of diffuse ALERD. However, these abnormalities are typically milder or absent in central-sparing ALERD. In our study, CSF abnormalities were noted in one case, while sepsis markers were positive in four children, with five having coexisting sepsis. It is noteworthy that inflammatory cytokine levels were not assessed in this study, which could have provided additional insights into the inflammatory response in ALERD.[3–5]

MRI plays a crucial role in diagnosing ALERD, with DWI revealing characteristic areas of restricted diffusion accompanied by edematous changes in cortical and subcortical regions.[6,7] In our study, radiological findings revealed a diffuse pattern in 66.7% and central sparing in 33.3% of ALERD patients (►**Table 1**). Diffuse ALERD is characterized by widespread areas of restricted diffusion on MRI, associated with severe clinical features and rapid deterioration of consciousness, often leading to coma and a relatively poor prognosis. In contrast, central-sparing ALERD presents with sparing of the central regions of the brain on MRI, resulting in a milder clinical picture with a biphasic course. This subtype typically starts with a prolonged seizure with fever, followed by an improvement in consciousness, although varying degrees of cognitive impairment can persist as neurological sequelae.[2–7]

The differential diagnosis of ALERD includes several conditions that can present with similar clinical and radiological features.

- Ischemia/infarction and encephalitis: These conditions can resemble ALERD, but differences in lesion distribution and CSF examination can aid in their differentiation.[8–10]
- Acute disseminated encephalomyelitis (ADEM): ADEM might manifest focal diffusion restriction but typically presents with larger, asymmetrical lesions involving deep and subcortical white matter in the cerebral hemispheres, cerebellum, and brainstem.[8–10]
- Febrile infection-related epilepsy syndrome (FIRES): Although initial MRI results might be normal in FIRES, signal changes may develop in gray matter structures, especially the mesial temporal lobes and hippocampi, with ongoing seizures.[8–10]
- Autoimmune encephalitis: MRI in autoimmune encephalitis could show normal findings or reveal limbic structure involvement and potentially affect other brain regions like the striatum, diencephalon, or rhombencephalon.[8–10]
- Mild leukoencephalopathy with reversible splenial lesion (MERS): MERS typically exhibits restricted lesions confined to the splenium of the corpus callosum and often presents with a milder clinical course.[8–10]

Table 1 Demographic, clinical characteristics, and MRI findings

Case	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age (mo)/ gender	12/M	48/F	20/M	15/M	8/F	23/M	42/F	37/F	29/M
Clinical course	Fever, vomiting, seizures, and altered sensorium	Relapsing fever, remitting pattern, seizures	Fever, vomiting, seizures, and altered sensorium	Relapsing fever, remitting pattern, seizures	Fever, vomiting, seizures, and altered sensorium	Fever, vomiting, seizures, and altered sensorium	Fever, vomiting, seizures, and altered sensorium	Fever, vomiting, seizures, and altered sensorium	Relapsing fever, remitting pattern, seizures
Disease course	Monophasic	Biphasic	Monophasic	Biphasic	Monophasic	Monophasic	Monophasic	Monophasic	Biphasic
Shock/MODS	Shock, AKI, and ALF	Shock, ALF	Shock	Shock	Shock	Shock, AKI, and ALF	Shock, ALF	Shock, ALF	Shock, ALF
Lab findings	Elevated TLC, viral markers negative, CSF analysis normal	Elevated TLC, dengue positive, CSF analysis normal	Elevated TLC, viral markers negative, CSF analysis normal	Elevated TLC, Dengue positive, CSF analysis normal	Elevated TLC, dengue positive, CSF analysis normal	Elevated TLC, viral markers negative, CSF analysis normal	Elevated TLC, viral markers negative, CSF analysis normal	Elevated TLC, dengue positive, CSF analysis lymphocyte predomi-nance	Elevated TLC, viral markers negative, CSF analysis normal
MRI brain findings	Diffuse type of ALERD	Central-sparing type of ALERD	Diffuse type of ALERD	Central-sparing type of ALERD	Diffuse type of ALERD	Diffuse type of ALERD	Diffuse type of ALERD	Diffuse type of ALERD	Central-sparing type of ALERD

Abbreviations: AKI, acute kidney injury; ALERD, acute leukoencephalopathy with restricted diffusion; ALF, acute liver failure; CSF, cerebrospinal fluid; F, female; M, male; MODS, multiple organ dysfunction syndrome; MRI, magnetic resonance imaging; TLC, total leukocyte count.

- Acute necrotizing encephalopathy (ANE): ANE may present with distinctive thalamic signal changes, helping to differentiate it from ALERD. Additionally, ANE can involve the brainstem, cerebellum, and white matter.[8–10]

Conclusion

ALERD is a distinct clinical-radiological syndrome characterized by acute encephalopathy, fever, prolonged seizures, and restricted diffusion on MRI. ALERD can be categorized into diffuse and central-sparing forms, each with unique clinical features and outcomes. The pathogenesis may involve hypercytokinemia, excitotoxic neuronal injury, and potential genetic predisposition factors. MRI, especially DWI, is crucial for diagnosing ALERD and revealing restricted diffusion areas. A thorough understanding of ALERD is essential for its accurate diagnosis and management.

Conflict of Interest
None declared.

References

1 Kamate M. Acute leukoencephalopathy with restricted diffusion. Indian J Crit Care Med 2018;22(07):519–523
2 Ranjan RS, Arya G, Yadav VK. Acute encephalopathy with biphasic seizures and late reduced diffusion (central sparing type)-MRI and MR spectroscopy findings. Indian J Radiol Imaging 2019;29 (04):426–430
3 Lawrence RM, Aripirala P, Reddy N, et al. The spectrum of acute leukoencephalopathy with restricted diffusion (ALERD): a case series and review of literature. Eur J Paediatr Neurol 2021; 33:86–93
4 Singh V, Tomar V, Kumar A, Phadke RV. Acute leucoencephalopathy with restriction of diffusion - a case report. East J Med 2012; 17:149–152
5 Tadokoro R, Okumura A, Nakazawa T, et al. Acute encephalopathy with biphasic seizures and late reduced diffusion associated with hemophagocytic syndrome. Brain Dev 2010;32(06):477–481
6 Schaefer PW, Grant PE, Gilberto Gonzalez R. Diffusion-weighted MR imaging of the brain. Radiology 2000;217(02):331–345
7 Takanashi J, Oba H, Barkovich AJ, et al. Diffusion MRI abnormalities after prolonged febrile seizures with encephalopathy. Neurology 2006;66(09):1304–1309, discussion 1291
8 Okumura A, Kidokoro H, Tsuji T, et al. Differences of clinical manifestations according to the patterns of brain lesions in acute encephalopathy with reduced diffusion in the bilateral hemispheres. AJNR Am J Neuroradiol 2009;30(04):825–830
9 Tada H, Takanashi JI, Terada H, Tajima K. Severe form of acute influenza encephalopathy with biphasic seizures and late reduced diffusion. Neuropediatrics 2008;39(02):134–136
10 Maeda M, Okanishi T, Miyamoto Y, et al. Predicting the onset of acute encephalopathy with biphasic seizures and late reduced diffusion by using early laboratory data. Front Neurol 2021; 12:730535

