J Pediatr Res 2025;12(2):108-113
DOI: 10.4274/jpr.galenos.2025.40222

Case Report

Tocilizumab in Dengue/Flavivirus-Associated Acute Necrotizing Encephalopathy: Two Pediatric Cases

Lokeswari Balleda, Sravani Kolla, Chandra Sekhara Reddy Thimmapuram

Sri Ramachandra Children's and Dental Hospital, Clinic of Pediatrics, Guntur, Andhra Pradesh, India

ABSTRACT

Acute necrotizing encephalopathy of childhood (ANEC) is a rare, rapidly progressive neurological disorder predominantly affecting children. It is often triggered by viral infections such as influenza. Dengue virus may also be a trigger. The hallmark of ANEC is cytokine storm-induced inflammation, leading to symmetrical necrotizing lesions in the thalami, brainstem, and cerebellum. Tocilizumab, an anti-interleukin 6 (IL-6) receptor antibody, has emerged as a promising therapy for cytokine-mediated damage. Here, we present 2 cases of dengue/flavivirus encephalopathy, "with magnetic resonance imaging findings suggestive of the classic features of ANEC", the symmetric bilateral lesions affecting the thalami. Two previously healthy children presented with acute febrile illness and neurological symptoms, requiring admission to a paediatric intensive care unit. The first case was a 5-year-old girl with a 3-day history of high fever, followed by seizures for 2 days and subsequent unconsciousness. Upon admission, she was critically ill, unconscious with a Glasgow Coma Scale score of E1M2V1, and in respiratory failure. Her acute necrotizing encephalitis severity score (ANE-SS) was 7/9. She was managed with ventilatory support, intravenous (IV) fluids, IV antibiotics, and other supportive care. The second case involved an 8-year-old boy with a 2-day history of fever, accompanied by headache, vomiting, and drowsiness. On admission, he was lethargic and drowsy, showing signs of meningeal irritation. His ANE-SS was 4/9. Both cases were treated with tocilizumab, an IL-6 receptor inhibitor, as a single dose of 12 mg/kg infusion over 1 hour, along with antiepileptics, corticosteroids, IV immunoglobulins, and other supportive management. Both patients recovered dramatically. Repeat neuroimaging on day 5 showed significant reductions in the sizes and severities of the lesions in both cases. The efficacy of tocilizumab in these two cases highlights its potential as a targeted therapy for cytokine-mediated neurological damage in ANEC.

Keywords: ANEC, dengue/flavivirus, tocilizumab

Introduction

Dengue is a mosquito-borne viral illness which affects millions globally, particularly in tropical regions. While it primarily manifests with fever, rash, and thrombocytopenia, dengue can also cause severe neurological complications, including encephalitis, myelitis, and, more rarely, acute necrotizing encephalopathy of childhood (ANEC) (1). ANEC is an rare but severe condition marked by rapid neurological decline and distinctive neuroimaging findings (2-4).

ANEC has a poor prognosis, with high mortality and severe neurological sequelae in survivors. The pathophysiology of ANEC involves a hyperimmune response to viral infections, characterized by a "cytokine storm" which disrupts the blood-brain barrier, leading to widespread brain damage. Tocilizumab, a monoclonal antibody which inhibits the interleukin-6 (IL-6) receptor, has been used in treating cytokine storm syndromes, and its role in managing ANEC associated with dengue is a promising new avenue (5,6).

Corresponding Author
Lokeswari Balleda, MD, Sri Ramachandra Children's and Dental Hospital, Clinic of Pediatrics, Guntur, Andhra Pradesh, India
E-mail: lballeda@gmail.com **ORCID:** orcid.org/0000-0003-4661-6145
Received: 26.01.2025 **Accepted:** 22.05.2025 **Publication Date:** 11.07.2025

Cite this article as: Balleda L, Kolla S, Thimmapuram CSR. Tocilizumab in dengue/flavivirus-associated acute necrotizing encephalopathy: two pediatric cases. J Pediatr Res. 2025;12(2):108-113

Case Report 1

A 5-year-old girl, previously healthy, presented with a high fever of 3 days duration, followed by seizures for 2 days with multiple episodes, followed by unconsciousness for 1 day. At the time of admission, the child was very sick, unconscious, with E1M2V1, and with respiratory failure. The patient was admitted to the paediatric intensive care unit. Treated with ventilatory support, intravenous (IV) fluids, IV antibiotics, and other supportive management. Investigations revealed hemogram (Hb) [Hb 10.2 gr %, packed cell volume (PCV) 27%, red blood cells (RBC) 4.2 million/cumm, white blood cells (WBC) 4,100 cells/cumm, (P47, L50, E03), platelets 197,000/cumm]. D-dimers 2,510 ng/mL, lactate dehydrogenase (LDH) 688 IU/L, procalcitonin 10.99 ng/mL, ferritin 442.5 ng/mL, IL-6 3.4 pg/mL, s. calcium 7.2 mg/dL, blood sugar 84 mg/dL, CRP 4.7 mg/L, s. sodium 132 mmol/L, s. potassium 4.0 mmol/L, s. chloride 99 mmol/L, s. creatinine 0.7 mg/dL, PT 12.8 sec, aPTT 32.6 sec, INR 0.9, s. bilirubin total 0.7 mg/dL and direct 0.4 mg/dL, serum glutamic-oxaloacetic transaminase (SGOT) 108 IU/L, serum glutamic-pyruvic transaminase (SGPT) 97 IU/L, alkaline phosphatase 81 IU/L, total protein 6.9 gr/dL, and albumin 3.8 gr/dL. Dengue enzyme-linked immunosorbent assay (ELISA) was positive for IgM. Electrocardiogram (ECG) and echocardiography (ECHO) were normal. Abdominal ultrasonography (USG) showed minimal ascites.

Neuroimaging via magnetic resonance imaging (MRI) revealed classic features of ANEC, with symmetric bilateral lesions affecting the thalami, cerebellar vermis, paravermian cerebellar hemisphere, right hippocampus, and left paraventricular region (differentials dengue/flaviviral encephalitis) (Figures 1, 2). Cerebrospinal fluid (CSF) analysis showed mildly elevated protein levels but no evidence of bacterial or other viral infections. Electroencephalogram (EEG) showed focal sharp discharges and slowing, diffuse monomorphic theta activity, poor sleep patterns, and diffuse cerebral dysfunction. The acute necrotizing encephalitis severity score (ANE-SS) was 7/9 [ANE-SS ranges from 0 to 9 points, with 3 points for the existence of shock, 2 points for brain stem lesions, 2 points for age over 48 months, 1 point for a platelet count below 100,000/µL, and 1 point for CSF protein above 60 mg/dL. Patients are classed as low risk (ANE-SS 0-1 points), medium risk (ANE-SS 2-4 points), or high risk (ANE-SS 5-9 points)] (7).

Despite standard supportive care, including antiepileptics, corticosteroids (methylprednisolone 30 mg/kg for 5 days), and IV immunoglobulins (2 gr/kg over 2 days), the child's condition continued to deteriorate. Given

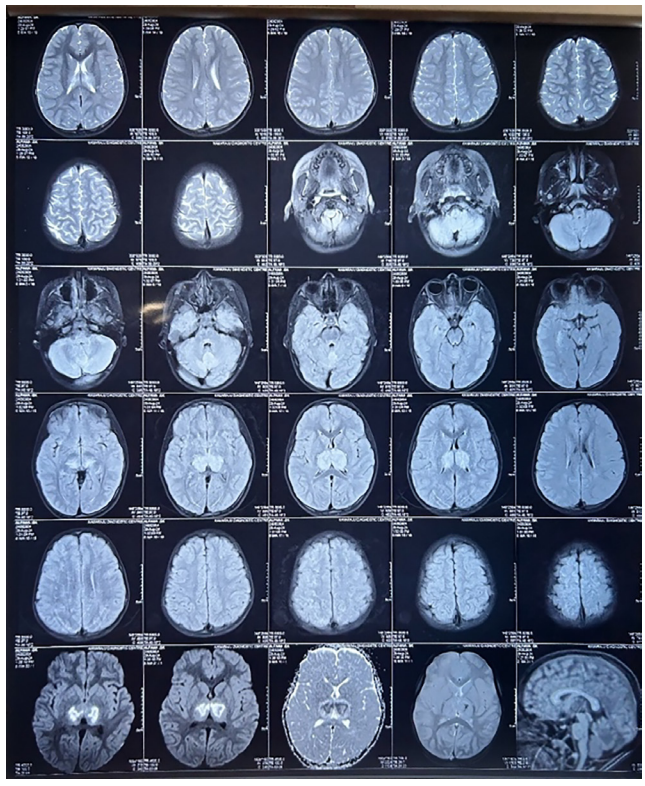

Figure 1. Areas of altered signal in thalami, cerebellar vermis, paravermian cerebellar hemisphere, right hippocampus, and left paraventricular region showing T2, FLAIR hyperintensity, T1 hypointensity with areas of diffusion restriction
FLAIR: Fluid-attenuated inversion recovery

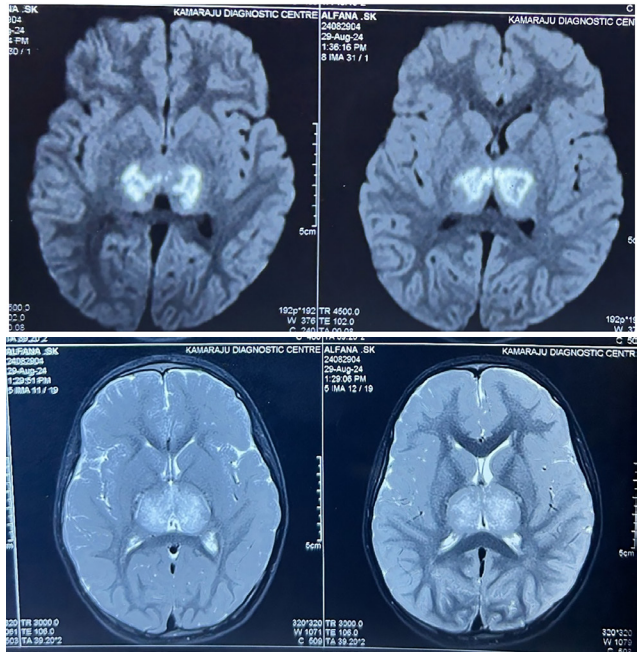

Figure 2. There are small foci of low signal on GE sequence in thalami suggesting hemorrhagic foci
GE: Gradient echo

the rapid progression of neurological damage and the suspected cytokine storm, the decision was made to initiate treatment with tocilizumab, an IL-6 receptor inhibitor. The patient received a single dose of 12 mg/kg of tocilizumab as an infusion over 1 hour. Within 36 hours, her seizures ceased, and her consciousness improved significantly. By day five, she was responsive, and her motor functions were gradually recovering. Repeat neuroimaging on day 5 showed a significant reduction in the size and severity of the lesions (Figure 3). The child was discharged with no significant neurological deficits and continued to do well on follow-up. After 1 month, she was completely normal with a normal MRI brain scan.

Case Report 2

An 8-year-old boy presented with a fever of 2 days duration, associated with headache, vomiting, and drowsiness. At the time of admission, the child was very sick, dull, drowsy, and with meningeal irritation. He was admitted to the paediatric intensive care unit. His ANE-SS was 4/9. He was treated with IV fluids, IV antibiotics, and other supportive management. Investigations revealed Hemogram [Hb 12.2 gr %, PCV 33%, RBC 4.4 million/cumm, WBC 5,900 cells/cumm, (P69, L28, E04), platelets 221,000/cumm].

D-dimers 5550 ng/mL, LDH 760 IU/L, Procalcitonin 22.82 ng/mL, ferritin 496.2 ng/mL, IL-6 2.0 pg/mL, s. calcium 7.2 mg/dL, blood sugar 116 mg/dL, CRP 8.9 mg/L, S. sodium 136 mmol/L, S. potassium 3.5 mmol/L, S. chloride 110 mmol/L, S. creatinine 0.7 mg/dL, PT 14.0 sec, aPTT 38.5 sec, INR 1.0, S. bilirubin total 0.6 mg/dL and direct 0.4 mg/dL, SGOT 29 IU/L, SGPT 22 IU/L, alkaline phosphatase 93 IU/L, total protein 6.9 gr/dL, and albumin 3.5 gr/dL. Dengue ELISA was positive for IgM. ECG and ECHO were normal. Abdominal USG showed minimal left hydronephrosis.

Neuroimaging via MRI revealed the classic features of ANEC, with symmetric bilateral lesions affecting the thalami (differentials dengue/flaviviral encephalitis) (Figure 4). CSF analysis showed a normal study. EEG showed

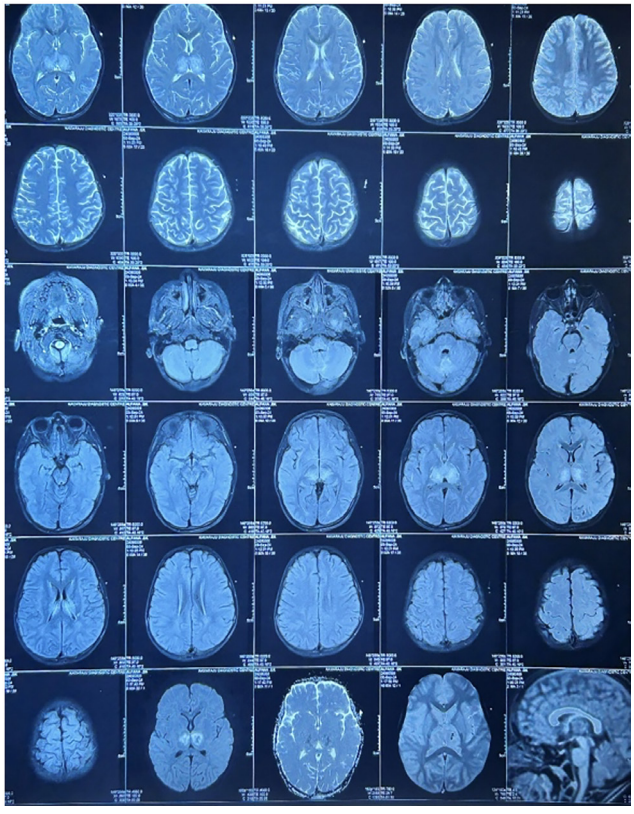

Figure 3. Areas of altered signal in the cerebrum and cerebellum. Partial resolution of signal changes in the cerebrum and cerebellum with no appearance of fresh changes

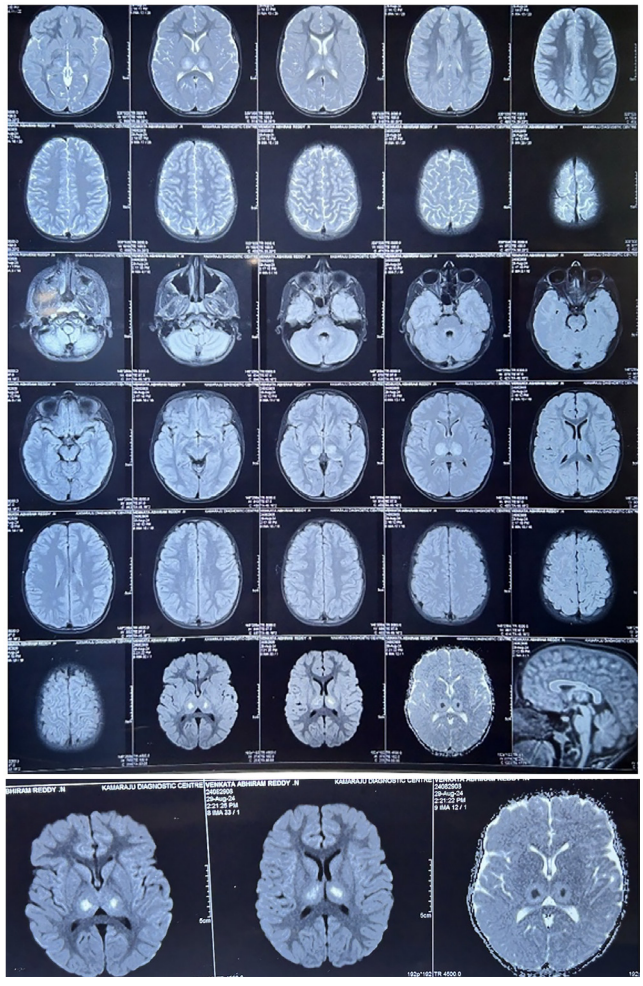

Figure 4. Bilateral relatively symmetrical areas of T2, FLAIR hyperintensity, T1 hypointensity with small areas of diffusion restriction in thalami
FLAIR: Fluid-attenuated inversion recovery

intermittent bursts of generalized slow-wave epileptiform discharges. Despite standard supportive care, including antiepileptics, corticosteroids (methylprednisolone 30 mg/kg for 5 days), and IV immunoglobulins (2 gr/kg over 2 days), the child's neurological condition deteriorated rapidly, likely due to a cytokine storm. As a result, the team administered a single dose of tocilizumab, an IL-6 receptor inhibitor, at 12 mg/kg as an infusion over 1 hour. Within 36 hours, the child's condition improved markedly, and by day 5, neuroimaging showed a significant reduction in lesion size and severity (Figure 5). The child was discharged without notable neurological deficits and continued to do well on follow-up.

Pathophysiology and Rationale for Tocilizumab

ANEC is thought to result from a hyperinflammatory response triggered by viral infections, which leads to excessive release of pro-inflammatory cytokines such as IL-6. This cytokine surge can compromise the blood-brain barrier, causing brain edema, haemorrhage, and necrosis, particularly affecting the thalami, brainstem, and cerebellum. The central role of the cytokine storm in ANEC's pathogenesis makes targeted immunotherapy a promising treatment approach. Tocilizumab, a monoclonal antibody which blocks IL-6 receptors, helps inhibit this cytokine surge and has shown positive outcomes in managing cytokine release syndromes in other conditions, such as coronavirus disease-2019 and autoimmune diseases. In these two cases, tocilizumab was administered early in dengue-associated ANEC, resulting in rapid neurological and radiological improvement, highlighting a novel therapeutic approach.

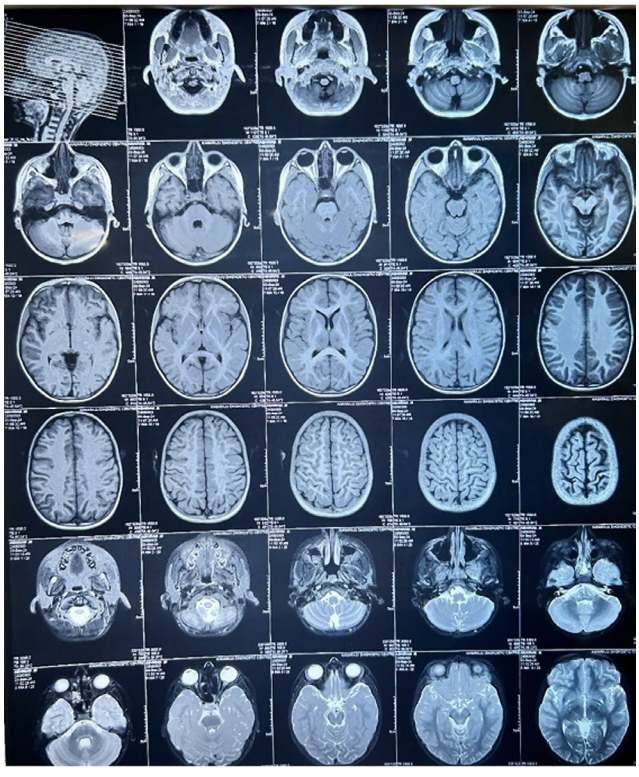

Figure 5. Reduction in the size of signal changes suggesting partial clearing

Tocilizumab is generally well tolerated. Its most common side effects include cough, sore throat, nasal congestion or runny nose, headache, dizziness, mouth ulcers, hypertension, hypercholesterolemia, allergic reactions, skin rashes, gastrointestinal symptoms, and haematological abnormalities such as cytopenias. It may also cause elevations in liver enzyme levels. Tocilizumab is contraindicated in individuals with known hypersensitivity to any of its components.

Management and Outcome

Both patients received standard supportive care, including antipyretics, fluid management, corticosteroids, and antiepileptic drugs. However, their neurological status continued to deteriorate until tocilizumab was introduced. In both cases, tocilizumab administration was followed by rapid clinical improvement, a stabilization of seizures, and a recovery of consciousness. Follow-up MRIs showed partial to significant resolution of the brain lesions, and both patients were discharged with minimal or no long-term neurological deficits.

The dramatic improvements seen in both patients underscore the potential role of tocilizumab in treating dengue-associated ANEC. Early intervention with tocilizumab may prevent the progression of brain injury and improve long-term neurological outcomes in this devastating condition.

Discussion

In our study, we demonstrated that early IL-6 blockade with tocilizumab in severe ANE is a safe treatment option and it may help improve outcomes. Our patients had thalamic lesions, which are key predictors of a high risk of death or severe disability based on the ANE severity score. Both patients showed excellent clinical and radiological recovery. By targeting the cytokine storm early, tocilizumab appears to reduce neurological damage and enable rapid clinical recovery. While corticosteroids are generally the first-line treatment used to decrease inflammation in ANEC, they may be insufficient in cases with intense cytokine storm activity.

Huang et al. (8), in their study, suggested that glucocorticoids and immunoglobulins may improve the prognosis of ANE. However, the underlying therapeutic mechanisms were not elaborated on, and both glucocorticoids and immunoglobulins lack specificity in the treatment of various critical illnesses. Therefore, their significance in the management of ANE remains questionable. In recent years, studies by Koh et al. (9) have reported the effective use of tocilizumab in mitigating cytokine storms.

Other studies have reported similar success with tocilizumab in treating severe neurological inflammation. Jaiswal et al. (10) described its use in a 24-month-old boy with acute leukoencephalopathy with restricted diffusion. On day 16 of treatment, the child received IV tocilizumab (8 mg/kg) after informed consent, leading to an improvement in sensorium and reduced irritability within 24 hours. The patient was then transitioned to oral prednisolone, tapered over three weeks. Similarly, Huang et al. (8) reported on a 2-year 10-month-old boy who developed ANE following a H1N1 (influenza A) infection. Post-tocilizumab treatment, the child experienced an improvement in consciousness, an absence of convulsions, enhanced limb mobility, and a significant reduction in encephalopathy lesions. Nguyen et al. (11) described the first known case of tocilizumab use in acute encephalopathy with biphasic seizures and restricted diffusion, involving a 21-month-old who received a single dose (120 mg) and achieved a normal outcome at six months.

In our study, we used tocilizumab at a dose of 12 mg/kg IV as a single dose. An open-label study by Mallalieu et al. (12) provided data on the pharmacokinetics, pharmacodynamics, and efficacy of tocilizumab 12 mg/kg IV in systemic juvenile idiopathic arthritis (sJIA) patients younger than 2 years, demonstrating comparability to patients aged 2 to 17 years. The safety profile was also similar, except for a higher incidence of serious hypersensitivity reactions in patients under 2 years of age.

Among other indications for tocilizumab use, Brunner et al. (13) conducted a 2-year clinical trial in patients aged 2 to 17 years with sJIA unresponsive to methotrexate. The patients received weight-based tocilizumab every 4 weeks, with responders at week 16 (n=166) randomized either to continue tocilizumab or switch to placebo until week 40, followed by open-label tocilizumab for all (n=160). At week 104, sustained therapeutic efficacy was demonstrated using JIA- American College of Rheumatology 50/70/90 response criteria (13).

Conclusion

ANEC is a rare but severe neurological complication of dengue fever, characterized by a cytokine storm which leads to rapid neurological deterioration with rapid onset encephalopathy and bilateral brain lesions. In this case report, two paediatric patients with dengue/flavivirus-associated ANEC improved dramatically after treatment with tocilizumab. These cases highlight the potential of IL-6 blockade to alter the course of this disease, offering hope for better outcomes in an otherwise grim prognosis. Further research and larger studies are warranted to explore the use of tocilizumab in this setting and to develop standardized treatment protocols for dengue-associated ANEC.

IL-6 blockade shows promise in managing severe dengue-associated ANEC: Tocilizumab, an IL-6 inhibitor, demonstrated significant clinical and radiological improvement in paediatric patients with dengue-associated ANEC, suggesting its potential to alter disease progression and improve outcomes in cases with a high risk of disability or mortality.

Rapid intervention can prevent further neurological deterioration: Early administration of tocilizumab helped manage cytokine storm-driven neurological damage, resulting in rapid improvement and underscoring the importance of timely intervention in cytokine-mediated encephalopathies.

Need for larger studies and standardized protocols: These cases underscore the urgent need for more research and larger studies in order to assess the efficacy and safety of tocilizumab in dengue-associated ANEC, ultimately contributing to the development of standardized treatment protocols to guide clinical practice.

Ethics

Informed Consent: Informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: L.B., Concept: L.B., Design: L.B., Data Collection or Processing: L.B., S.K., C.S.R.T., Analysis or Interpretation: L.B., S.K., C.S.R.T., Literature Search: L.B., S.K., C.S.R.T., Writing: L.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Kumar S, Navid A, Sharma R, Suthar R, Vyas S, Angurana SK. Acute necrotizing encephalopathy of childhood: a rare neurological manifestation of dengue. Ann Indian Acad Neurol. 2021; 24:828-31.
2. Trivedi S, Chakravarty A. Neurological complications of dengue fever. Curr Neurol Neurosci Rep. 2022; 22:515-29.
3. World Health Organization. Dengue: Guidelines for diagnosis, treatment, prevention and control. 2nd ed. Geneva: World Health Organization; 2009.
4. Barron S, Han VX, Gupta J, Lingappa L, Sankhyan N, Thomas T. Dengue-associated acute necrotizing encephalopathy is an acute necrotizing encephalopathy variant rather than a mimic: evidence from a systematic review. Pediatr Neurol. 2024; 161:208-15.
5. Fan X, Huang L, Li S, et al. Clinical evaluation of acute necrotizing encephalopathy in children. Front Pediatr. 2022; 10:947693.
6. Gupta J, Choudhary R, Gupta A, et al. Child neurology: Acute necrotizing encephalopathy of childhood associated with dengue: Good neurologic outcome despite a fulminant presentation. Neurology. 2024; 103:e209954.
7. Yamamoto H, Okumura A, Natsume J, Kojima S, Mizuguchi M. A severity score for acute necrotizing encephalopathy. Brain Dev. 2015; 37:322-7.
8. Huang Y, Zhou B, Hong S, Cai Y. A case report and literature review on tocilizumab-cured acute necrotizing encephalopathy caused by influenza A virus. Front Pediatr. 2024; 12:1351478.
9. Koh JC, Murugasu A, Krishnappa J, Thomas T. Favorable outcomes with early ınterleukin 6 receptor blockade in severe acute necrotizing encephalopathy of childhood. Pediatr Neurol. 2019; 98:80-4.
10. Jaiswal A, Patel S, Khare S, Passi GR. Tocilizumab in a child with acute leukoencephalopathy with restricted diffusion. ann indian acad neurol. 2023; 26:95-6.
11. Nguyen KL, McGurty D, Innes EA, et al. Acute encephalopathy with biphasic seizures and restricted diffusion. J Paediatr Child Health. 2022; 58:1688-90.
12. Mallalieu NL, Wimalasundera S, Hsu JC, et al. Intravenous dosing of tocilizumab in patients younger than two years of age with systemic juvenile idiopathic arthritis: results from an open-label phase 1 clinical trial. Pediatr Rheumatol Online J. 2019; 17:57.
13. Brunner HI, Ruperto N, Zuber Z, et al. Efficacy and safety of tocilizumab for polyarticular-course juvenile idiopathic arthritis in the open-label two-year extension of a phase III trial. Arthritis Rheumatol. 2021; 73:530-41.