Dear Editor

Dengue is a common arboviral infection in India and it classically presents with fever, arthralgia, headache, rash, bleeding manifestations, and features of capillary leak. Expanded dengue can involve almost all the systems. The neurological complications are uncommon in dengue with a reported incidence of 0.5%–28% including seizures, intracranial bleeding, encephalopathy, meningoencephalitis, acute disseminated encephalomyelitis (ADEM), Guillain-Barre syndrome, transverse myelitis, and rarely acute necrotizing encephalopathy of childhood (ANEC) and hemiconvulsion hemiplegia epilepsy.\cite{1-4}

ANEC is a rare clinico-radiological entity leading to acute onset febrile encephalopathy with rapid progression and is associated with poor outcome. ANEC is caused by para-infectious trigger mainly viruses including influenza, human herpes virus-6, parainfluenza, human herpes virus-7, varicella, enterovirus, novel reovirus strain, rotavirus, herpes simplex virus, rubella, coxsackie A9, and measles. Other causes include mycoplasma, immune-mediated, and genetic or familial (RANBP2 mutation).\cite{5-8} The neurological injury is possibly due to direct viral injury, immune-mediated injury, or cytokine storm leading to blood–brain barrier damage, edema, congestion, and hemorrhage, without any signs of direct viral invasion or postinfectious demyelination.\cite{6,7,9} The literature on ANEC in association with dengue is limited.\cite{10} The rarity of ANEC in association with dengue and good neurological recovery with supportive treatment made us to report this case.

A 6-year-old male presented with fever for 4 days, vomiting, and altered sensorium for 2 days. Examination revealed weight 18 kgs; respiratory rates 40/min; features of compensated shock (pulse rate 132/min, palpable central pulses, weak peripheral pulses, prolonged capillary refill time, and blood pressure 88/58 mmHg); pallor, bleeding from nasal and oral mucosa, and hepatomegaly. Central nervous examination revealed low Glasgow Coma Scale (9/15), intermittent extensor posturing, brisk deep tendon reflexes, extensor planter reflexes (features suggestive of raised intracranial pressure, ICP); and normal-sized and reacting pupils, no signs of meningeal irritation, and normal fundus examination. The initial management included fluid boluses, vasoactive drugs, mechanical ventilation, intravenous antibiotics (ceftriaxone, doxycycline, and acyclovir), sedation and analgesia, and measures to lower raised ICP.

Investigations revealed blood glucose 115 mg/dL, hemoglobin 10.1 gm/dL, total leucocyte count 22700/cumm, platelet count 51,000/cumm, serum sodium 139 meq/L, potassium 4 meq/L,
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urea 64 mg/dL, creatinine 0.95 mg/dL, bilirubin 0.56 mg/dL, SGOT 19301 IU/L, SGPT 4807 IU/L, protein 5.6 gm/dL, albumen 3.3 gm/dL, procalcitonin 1.5 ng/ml, ferritin 480 ng/ml, ammonia 72 (µmol/L), prothrombin time 27 seconds, prothrombin index 55%, activated prothrombin time 43 seconds, INR 1.8, and fibrinogen 1.75 mg/dL [Table 1]. Noncontrast CT head revealed hypodensities in bilateral thalami [Figure 1a]. Cerebrospinal fluid (CSF) analysis revealed 13 cells/cumm (30% neutrophils and 70% lymphocytes), protein 94 mg%, glucose 75 mg%, sterile culture, and negative herpes simplex virus DNA PCR. The dengue NS1 antigen and IgM antibodies were positive in blood. The scrub typhus serology, hepatitis B surface antigen, hepatitis A IgM antibody, hepatitis E IgM antibody, hepatitis C IgM antibody, nasopharyngeal swab for H1N1 PCR were negative. MRI brain (on day 5) showed altered signal intensities with diffusion restriction and interspersed hemorrhages in bilateral thalami, putamen, and midbrain [Figure 1b-e]. Similar changes were also seen involving pons and medulla.

Based on the temporal evolution of clinical features, laboratory parameters, and radiological findings, a diagnosis of ANEC associated with dengue infection was considered. He developed central line-associated bloodstream infection (CLABSI) due to Acinetobacter baumannii which was treated with colistin for 10 days. With supportive treatment, there was a gradual improvement in neurological status and laboratory parameters [Table 1]. The plan to give methylprednisolone was withheld in view of active infection (CLABSI) in the first week and later due to clinical recovery. He was extubated on day 10 and discharged after 21 days of hospital stay with a pediatric cerebral performance category score (PCPC) of 4. On 3 months follow-up, the PCPC score was 2.

We described a child with expanded dengue associated with ANEC who recovered with supportive treatment. ANEC usually affects younger children and commonly reported in association with respiratory viruses[5-7] and its association with dengue virus is rarely reported.[4]

The proposed diagnostic criteria for ANEC include acute onset of encephalopathy with rapid neurological deterioration; CSF examination showing increased protein with no pleocytosis; neuroimaging showing bilateral symmetrical involvement of the thalamus, internal capsule, putamen, cerebellum,

### Table 1: Laboratory parameters

| Date | Day 1 | Day 2 | Day 3 | Day 5 | Day 7 | Day 9 | Day 12 |
|------|-------|-------|-------|-------|-------|-------|-------|
| Hb (gm/dL) | 10.1 | 8.2 | 10.4 | 10 | 8 | 8.2 | 8.5 |
| TLC (per cumm) | 22700 | 19200 | 14630 | 11720 | 6600 | 10880 | 11000 |
| Platelets (per cumm) | 51000 | 84000 | 104000 | 90000 | 71000 | 132000 | 232000 |
| Sodium (meq/L) | 139 | 141 | 156 | 151 | 138 | 135 | 138 |
| Potassium (meq/L) | 4 | 4.7 | 5.6 | 3.3 | 3.7 | 4.9 | 4.7 |
| Urea (mg/dL) | 64 | 95 | 93 | 69 | 41 | 36 | 39 |
| Creatinine (mg/dL) | 0.95 | 1.4 | 1.6 | 0.8 | 0.4 | 0.3 | 0.4 |
| Bilirubin (mg/dL) | 0.56 | 0.4 | 0.42 | 0.69 | 0.6 | 0.56 | 0.5 |
| SGOT (IU/L) | 19301 | 10468 | 3999 | 1168 | 200 | 232 | 80 |
| SGPT (IU/L) | 4807 | 1953 | 1442 | 842 | 317 | 105 | 92 |
| Serum protein (gm/dL) | 5.6 | 5.1 | 5.2 | 5.7 | 5.3 | 5.6 | 6.8 |
| Serum albumin (gm/dL) | 3.3 | 2.8 | 2.8 | 3.1 | 2.7 | 2.7 | 3.6 |
| Procalcitonin (ng/mL) | 1.5 | 480 |
| Serum ferritin ( ) | 72 |
| Ammonia (µmol/L) | 27 | 12 |
| PT (seconds) | 55 | 100 |
| PTI (%) | 43.1 | 34.9 |
| aPTT (seconds) | 1.8 | 1.25 |
| INR | 1.75 |

![Figure 1: (a) Non contrast CT head revealed hypodensities in bilateral thalami. Axial T1 (b), T2 (c and e) and FLAIR (d) MR images showing confluent areas of altered signal intensities in form of T2/FLAIR hyper-intensities and T1 hypointensity involving bilateral thalami and putamen (b-d) and midbrain (e). These lesions showed diffusion restriction and susceptibility changes suggestive of haemorrhagic foci](image-url)
brainstem, and periventricular white matter; elevated serum transaminases; normal blood ammonia; and exclusion of other viral/bacterial infections, Reye’s syndrome, Leigh disease, ADEM, and vasculitis.[6,10]

The differential diagnosis in the index child could be encephalopathy or encephalitis associated with dengue. Encephalopathy is diffuse involvement of the brain without any specific or focal finding on imaging and commonly occurs due to systemic dysfunction (shock, liver dysfunction, coagulopathy, and sepsis). Encephalitis occurs due to direct viral invasion and inflammation of brain parenchyma and characterized by focal abnormalities on neuroimaging.[6,13] The imaging findings of dengue encephalitis are non-specific and common reported findings include diffuse cerebral edema, involvement of thalami, pons, and medulla (FLAIR and T2 hyperintensities) with heterogeneous or peripheral contrast enhancement, diffusion restriction in few areas, and petechial hemorrhages.[11-13]

Though, dengue encephalitis could be a differential diagnosis, the presence of shock, liver dysfunction, renal dysfunction, and bilateral symmetrical involvement of thalami point more towards ANEC associated with dengue. The characteristic involvement of the thalamus is described in form of trilaminar, target, or tricolar pattern on apparent diffusion coefficient images that occur due to central hemorrhage and necrosis, surrounded by cytotoxic edema and vascular congestion, and peripheral vasogenic edema.[9]

Though there are no standard guidelines for the treatment of ANEC, the commonly used modalities include antiviral drugs, steroids, intravenous immunoglobulins, plasmapheresis, antithrombin III, and therapeutic hypothermia.[6,8,14] Okumura et al.[14] in a retrospective study demonstrated that the administration of steroids within 24 h of onset of encephalopathy was associated with better outcomes in children with ANEC without brainstem lesions, but they did not find much benefit of IVIG. Most often, the children with ANEC are managed with the administration of steroids ± IVIG.[8,15,16]

The outcome of ANEC is generally poor, with high mortality (30%–40%) and survivors used to have moderate to severe disability, and complete recovery is seen in <10% of children.[4,9] The good recovery in index child (without specific treatment) may be due to aggressive intensive and supportive care, and neuroprotective strategies in the pediatric intensive care unit.

Though the proposed criteria suggest the exclusion of viral/bacterial infections to diagnose ANEC, it must be remembered that ANEC is usually caused by para-infectious trigger mainly viruses. Similar to the index case, Abbas et al.[4] reported a 15-year-old female who presented with a short history of fever, headache, seizure, encephalopathy, and shock. Investigations revealed thrombocytopenia, transaminitis, positive dengue IgM, and T1 hypo- and T2 hyper-intense signals symmetrically involving the thalamus, midbrain, pons, and cerebellar white matter with minimal contrast enhancement and diffusion restriction on MRI brain. She died despite treatment with vasoactive drugs, mechanical ventilation, neuroprotective strategies, methylprednisolone, and intravenous immunoglobulin. Here also, the ANEC was diagnosed in the presence of active Dengue infection. To the best of our knowledge, this is the first report of ANEC associated with dengue infection with good neurological outcome.

The ANEC in association with dengue is an uncommon occurrence. In endemic regions, dengue should be considered in children presenting with acute febrile illness and neurological manifestations.

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Conflicts of interest
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REFERENCES
1. Carod-Artal FJ, Wichmann O, Farrar J, Gascon J. Neurological complications of dengue virus infection. Lancet Neurol 2013;12:906-19.
2. Sil A, Biswas T, Samanta M, Konar MC, De AK, Chaudhuri J. Neurological manifestations in children with dengue fever: An Indian perspective. Trop Doct 2017;47:145-9.
3. Saini L, Chakrabarty B, Pastel H, Israni A, Kumar A, Gulati S. Dengue fever triggering hemiconvulsion hemiplegia epilepsy in a child. Neurrol India 2017;65:636-8.
4. Abbas Q, Jafri SK, Ishaque S, Jamil MT. Acute necrotizing encephalopathy of childhood secondary to Dengue infection: A case report from Pakistan. J Pediat Neurolsci 2017;12:165-7.
5. Jan F, Jafri SK, Ibrahim SH. Acute necrotizing encephalopathy. J Coll Physicians Surg Pak 2019;29:649-53.
6. Mizuguchi M. Acute necrotizing encephalopathy of childhood: A novel form of acute encephalopathy prevalent in Japan and Taiwan. Brain Dev 1997;19:81-92.
7. Wu X, Wu W, Pan W, Wu L, Liu K, Zhang HL. Acute necrotizing encephalopathy: An underrecognized clinicoangiographic disorder. Mediators Inflamm 2015;2015:792578.
8. Sondhi V, Chakrabarty B, Kumar A, Kohli S, Saxena R, Verma IC, et al. RANBP2 mutation in an Indian child with recurrent acute necrotizing encephalopathy. Brain Dev 2016;38:937-42.
9. Wong AM, Simon EM, Zimmerman RA, Wang HS, Toh CH, Ng SH. Acute necrotizing encephalopathy of childhood: Correlation of MR findings and clinical outcome. AJNR Am J Neuroradiol 2006;27:1919-23.
10. Kim JH, Kim IO, Lim MK, Park MS, Choi CG, Kim HW, et al. Acute necrotizing encephalopathy in Korean infants and children: Imaging findings and diverse clinical outcome. Korean J Radiol 2004;5:171-7.
CIA and CIN are defined when the absolute leukocyte count falls below 3,500/mm³, and neutrophil counts are lower than or equal to 3,500/mm³.

The prevalence of CIA, reported in a large cohort of patients in the USA, was 0.5–2% and CIN 3%.

The mechanism of CIA/CIN is largely unknown, but it is inconsistent in the published literature. In general, the cut-off values in the absolute counts, even if these remain above the normal range, treatment with clozapine should be permanently discontinued and clozapine can be resumed if the count returns to normal. Treatment should be permanently discontinued if the leukocyte or neutrophil counts fall below 2,000/mm³.

Close monitoring (ideally daily testing) of blood counts is necessary. If the absolute leukocyte count falls below 1,500/mm³ or absolute neutrophil count falls below 1,000/mm³, treatment with clozapine should be interrupted. Recent evidence suggests, approximately 75% of patients with mild CIN will not progress to moderate–severe CIN.

The grading of severity of CIA and CIN is currently no uniform monitoring protocol. Hence, we undertook a retrospective medical record review (digitally archived OPD charts and lab records) of patients treated with low-dose clozapine in a regional movement disorders (MD) clinic. The Institutional Ethics Committee approved the study.

Outcomes of acute necrotizing encephalopathy of childhood with H1N1 infection: A review. J Neurol Sci 2014;346:26-34.

Sonik BK, Das DSR, George RA, Aggarwal R, Sivasankar R. MRI features in dengue encephalitis: A case series in South Indian tertiary care hospital. Indian J Radiol Imaging 2017;27:125-8.

Rastogi R, Garg B. Findings at brain MRI in children with dengue fever and neurological symptoms. Pediatr Radiol 2016;46:139-44.

Okumura A, Mizuguchi M, Kidokoro H, Tanaka M, Abe S, Hosoya M, et al. Outcome of acute necrotizing encephalopathy in relation to treatment with corticosteroids and gammaglobulin. Brain Dev 2009;31:221-7.

Takia L, Patra N, Nallasamy K, Saini L, Suthar R, Angurana SK, et al. Acute necrotizing encephalopathy of childhood with H1N1 infection. J Pediatr Intensive Care 2020;9:222-4.

Takia L, Saini L, Keshavan S, Angurana SK, Nallasamy K, Suthar R, et al. Neurological manifestations of influenza A (H1N1): Clinical features, intensive care needs, and outcome. Indian J Pediatr 2020;87:803-9.

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11. Verma R, Sahu R, Holla V. Neurological manifestations of dengue infection: A review. J Neurol Sci 2014;346:26-34.
12. Sonik BK, Das DSR, George RA, Aggarwal R, Sivasankar R. MRI features in dengue encephalitis: A case series in South Indian tertiary care hospital. Indian J Radiol Imaging 2017;27:125-8.
13. Rastogi R, Garg B. Findings at brain MRI in children with dengue fever and neurological symptoms. Pediatr Radiol 2016;46:139-44.
14. Okumura A, Mizuguchi M, Kidokoro H, Tanaka M, Abe S, Hosoya M, et al. Outcome of acute necrotizing encephalopathy in relation to treatment with corticosteroids and gammaglobulin. Brain Dev 2009;31:221-7.
15. Takia L, Patra N, Nallasamy K, Saini L, Suthar R, Angurana SK, et al. Acute necrotizing encephalopathy of childhood with H1N1 infection. J Pediatr Intensive Care 2020;9:222-4.
16. Takia L, Saini L, Keshavan S, Angurana SK, Nallasamy K, Suthar R, et al. Neurological manifestations of influenza A (H1N1): Clinical features, intensive care needs, and outcome. Indian J Pediatr 2020;87:803-9.

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