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Review Article

Acute necrotising encephalopathy of childhood – A narrative review

Bidisha Banerjee[1], Ullas V. Acharya[2]

Departments of [1]Pediatric Neurology and [2]Pediatrics and Radiology, Manipal Hospitals, Bengaluru, Karnataka, India.

***Corresponding author:**
Bidisha Banerjee,
Department of Pediatric Neurology, Manipal Hospitals, Bengaluru, Karnataka, India.

drbidisha@yahoo.co.in

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ABSTRACT

Acute encephalitis syndrome (AES) can pose challenges in diagnosis and management. Infection-associated acute encephalopathies (AEs) are increasingly being recognised and closely mimic AES. We provide an overview of various causes of AE and a detailed review of the clinical laboratory, including neuroradiologic features of acute necrotising encephalopathy (ANE) of childhood, its treatment, and outcome. A literature search was performed using the keywords' Paediatric acute encephalopathy' and 'acute necrotising encephalopathy of childhood' in PubMed and Google Scholar, and all relevant articles from 2001 to 2021 (including case reports) in the English language were reviewed. Relevant and major articles before 2001 were also reviewed. Infection-associated AEs remain under-recognised and pose a challenge in neurocritical care. Judicious use of neuroimaging and laboratory tests aids diagnosis of specific clinicoradiological AE syndromes. We need to suspect ANE if fever (esp. viral illness) is followed by the rapid deterioration in the sensorium associated with tone abnormalities or seizures. Neuroimaging typically shows symmetric lesions in the thalami, internal capsule or cerebellar white matter and tegmentum. While definite treatment guidelines are not available, several interventions have shown potential benefits in supporting patients with ANE. These include standard supportive care, immunotherapy, especially high-dose pulse methylprednisolone, therapeutic hypothermia initiated before 12 h to reduce cytokines, and anti-oedema measures. However, it is essential to note that outcomes in ANE can be highly variable, with a mortality rate of approximately 30% and only 10% experiencing intact survival. Predictors of poor outcome include age younger than one year, increased cerebrospinal fluid protein/transaminases, the presence of haemorrhage/cavitation/brainstem lesions on neuroimaging, and a high ANE severity score.

Keywords: Acute encephalopathy, Acute necrotising encephalopathy of childhood, Acute necrotising encephalopathy, Neuroimaging

AIMS AND BACKGROUND

Acute encephalopathy (AE) constitutes an important medical emergency. Infections contribute to a large majority of AE. Moreover, infection-associated encephalopathies are increasingly being recognised with the wide use of neuroimaging. Recognition of the cause of AE or a specific syndrome helps in management and counselling. In this review, a brief overview of the various infection-associated encephalopathies is followed by a more detailed review of acute necrotising encephalopathy (ANE).

OVERVIEW OF INFECTION-ASSOCIATED AE SYNDROMES OF CHILDHOOD

AE refers to an acute onset of impairment of consciousness lasting for a duration of 24 hours or longer.[1] It is a complication of infectious diseases with potential morbidity and mortality.

While there are many causes of AE, it is usually seen in the context of infectious diseases. Cerebral oedema often accompanies which can be assessed on neuroimaging.

Encephalopathy needs to be distinguished from encephalitis. Encephalitis is characterised by an acute onset of fever and encephalopathy with or without seizures or other neurological signs resulting from inflammation of the central nervous system (CNS). On the other hand, encephalopathy is non-inflammatory; hence, cerebrospinal fluid (CSF) does not show pleocytosis.

Although AE may occur in any age group, but is more common in infants and young children during the acute stage of febrile infectious illness.

Neuroimaging with cranial computed tomography (CT) and magnetic resonance imaging (MRI) aids in the identification of cerebral oedema. Sequences on MRI, such as diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps, are sensitive and help to distinguish vasogenic from cytotoxic oedema.

AE is an umbrella term including many heterogeneous clinicoradiologic/pathologic syndromes.[1] They include AE caused by a metabolic disorder, AE caused by cytokine storm, AE with convulsive status epilepticus/excitotoxicity, and miscellaneous syndromes [Table 1].

A rapid syndromic diagnosis of AE and prompt intensive and supportive care are needed to improve outcomes. Prolonged or worsening impairment of consciousness and seizures, cerebral oedema on neuroimage, abnormal patterns on electroencephalogram such as diffuse, high amplitude slowing and absence of physiological markers of sleep will suggest AE. In addition, certain features can be observed in AE syndromes. These include elevated liver transaminases, such as serum aspartate aminotransferase and alanine aminotransferase, metabolic acidosis, leukocytosis, decreased platelet count, and increased CSF protein levels. It is crucial to distinguish AE syndromes from other conditions that may present with acute impairment of consciousness during the course of infectious diseases. For example, AE with biphasic seizures and late reduced diffusion (AESD) should be differentiated from febrile status epilepticus/complex febrile seizures, while ANE associated with multiple organ involvement (cytokine storm) should be distinguished from systemic inflammatory response syndrome (SIRS) caused by severe infection. Furthermore, Reye syndrome should be differentiated from inherited metabolic disorders. Characteristic MRI findings are an integral part of the diagnostic criteria for ANE, AESD, and mild encephalopathy with reversible splenial lesions, all of which present with infection-associated AE.[1]

Methods

Literature search was performed using the keywords' Paediatric acute encephalopathy' and 'acute necrotising encephalopathy of childhood (ANEC)' in PubMed and Google Scholar, and all relevant articles from 2001 to 2021 (including case reports) in the English language were reviewed. Prominent articles before 2001 were also reviewed. Herein, we review the aetiopathogenesis, clinical presentation, diagnosis, treatment, and prognosis of ANEC.

Acute necrotising encephalopathy of childhood (ANEC)

Introduction

ANEC is a potentially debilitating AE characterised by bilateral symmetric thalamic lesions and fever. Symptoms of ANE include rapidly progressing altered sensorium, seizures, tonic posturing, and vomiting. Liver dysfunction is commonly observed in affected individuals. CSF analysis typically shows increased protein without pleocytosis. ANE often exhibits high mortality and morbidity rates.[2] Initially described in Japan, Taiwan, and Korea,[3-5] cases are increasingly reported worldwide, including in India.[6-9] ANE is relatively rare and can be mistaken for conditions such as febrile seizures and acute encephalitis syndrome, leading to delayed diagnosis.

The aetiopathogenesis of ANE is not fully understood, but many pathogens, particularly viruses, have been associated with the condition. Despite this, the exact pathomechanism remains unknown. ANEC has been etiologically associated with viruses such as Influenza A, influenza B, novel influenza A (H1N1), herpesvirus (HHV)-6, dengue, parainfluenza, varicella, HHV-6 and HHV-7, enterovirus, rotavirus, herpes simplex virus, rubella, and coxsackie A9.[2,4,9-12] Recently, COVID-19 has been associated with ANEC.[13] No difference has been noted with regard to aetiology except for more frequent brain stem lesions in ANEC secondary to influenza.[14] Familial or recurrent ANEC due to mutations in the gene encoding the nuclear pore protein Ran Binding Protein 2 has also been reported, implying the role of host susceptibility.[15] This gene accounts for 3/4th of familial cases and has a dominant inheritance with incomplete penetrance. Human leukocyte antigen (HLA) DRB/HLA DQB genes might play a role in the pathogenesis of ANE.[2] The most prevalent hypothesis is hypercytokinemia, commonly known as the 'cytokine storm'. According to current understanding, an infection-induced aberrant immune response triggers an exaggerated production of cytokines, including tumour necrosis factor-alpha (TNF-α), interleukin (IL)-1 and IL-6, leading to brain and other organ injuries, such as liver dysfunction, acute renal failure, shock and disseminated intravascular coagulation (DIC). This abnormal immune response also results in altered vessel wall

Table 1: Summary of infection-associated AE syndromes.

Pathomechanism	AE syndromes	Clinical and laboratory characteristics	Radiologic features
AE caused by metabolic disorder	Reye syndrome	Viral infection (usually influenza or varicella) and/or salicylate use tiggers encephalopathy (vomiting, irritable to coma) with liver involvement (hyperammonemia, hypoglycaemia)	Cerebral oedema
	Intoxication phenotype of inborn errors of metabolism	Progressive encephalopathy with high anion gap metabolic acidosis/hyperammonemia/lactic acidosis/hypoglycemia	Metabolic stroke-like lesions in basal ganglia, occipital cortex, watershed areas
AE caused by cytokine storm	ANE	Rapidly worsening encephalopathy and raised liver enzymes without hyperammonemia (details in text)	Symmetric thalamic lesions, lesions in cerebral and cerebellar white matter and brain stem tegmentum
	HSES	Previously healthy infants with sudden onset encephalopathy, shock, coagulopathy and multiorgan dysfunction with metabolic acidosis. High mortality and morbidity.	Cytotoxic oedema in watershed zones of MRI.
AE with CSE	AESD	Febrile status epilepticus followed by reappearance of seizure clusters (focal) after day 3. Variable outcomes usually high morbidity	Early normal MRI with delayed cytotoxic oedema of subcortical white matter (bright-tree appearance)
	Acute infantile encephalopathy predominantly affecting the frontal lobes	Similar to AESD with predominant involvement of frontal lobes in young infants.	Cytotoxic oedema in frontal lobes
	HHE syndrome	Fever and Status epilepticus followed by neurologic sequelae hemiparesis and refractory epilepsy	Acute hemispheric cytotoxic oedema followed by cerebral hemiatrophy
	FIRES/AERRPS	Febrile illness followed by focal seizures involving face (eye deviation, hemifacial twitch) evolving to super-refractory status epilepticus. Associated with CSF pleocytosis, interictal periodic discharges on EEG. Chronic residual epilepsy.	MRI abnormalities on hippocampus, periinsular cortex, claustrum, thalamus or basal ganglia. Chronic cerebral atrophy.
Miscellaneous AE syndromes	Clinically MERS	Delirious behaviour (may be intermittent), consciousness disturbance or seizures within 1 week after fever, neurological symptoms persisting for more than 12 h. Usually complete recovery within 1 month after onset. Exclusion of other neurological diseases such as ADEM, AESD.	DWI showing a reversible splenial lesion with homogeneously reduced diffusion with mild T1 and T2 signal abnormalities. Lesion involving at least the splenium. It may expand to the entire corpus callosum or symmetrical white matter. Lesion disappears within 2 months, leaving no abnormal signal or atrophy.

CSF: Cerebrospinal fluid, MRI: Magnetic resonance imaging, AE: Acute encephalopathy, ANE: Acute necrotising encephalopathy, HSES: Haemorrhagic shock and encephalopathy syndrome, CSE: Convulsive status epilepticus, HHE: Hemiconvulsion-hemiplegia-epilepsy, FIRES: Febrile infection-related epilepsy syndrome, AERRPS: Acute encephalitis with refractory, repetitive partial seizures, EEG: Electroencephalography, ADEM: Acute disseminated encephalomyelitis, DWI: Diffusion-weighted imaging, MERS: Mild encephalopathy with reversible splenial lesion, AESD: Acute encephalopathy with biphasic seizures and late reduced diffusion

permeability, contributing to brain injury. In addition, high concentrations of IL-6 exhibit neurotoxic effects, while TNF-α can damage the endothelium of the CNS. Hypercytokinemia further disrupts the blood-brain barrier (BBB) through the action of trypsin and matrix metalloprotease-9, thereby increasing vessel wall permeability and resulting in cerebral oedema, haemorrhage, and necrosis.[2]

Clinical presentation

Patients with ANE do not exhibit specific symptoms or typical neurological signs, and the disease's clinical features have been consistent worldwide. Alongside prodromal symptoms due to viral infections, which may include fever, signs of upper respiratory tract infections, gastroenteritis,

and erythema, ANE patients often present signs of SIRS such as shock, multiple organ dysfunction, and DIC. Neurological dysfunction in ANE manifests as seizures, rapidly progressing disturbance of consciousness, tonic posturing, and less commonly, focal neurological deficits.[4]

Diagnosis

The diagnosis of ANEC is based on clinical symptoms, laboratory and neuroimaging findings, as proposed by Mizuguchi in 1995.[4] In the diagnosis of ANE, bilateral symmetric lesions in thalami, particularly, are invaluable [Table 2]. Mizuguchi suggested the following diagnostic criteria for sporadic ANE:

AE is related to a febrile viral infection, characterised by rapid reduction of consciousness and seizures.

CSF examination showed a normal cell count and increased protein concentration.

The presence of symmetrical and multiple brain lesions on head CT and/or MRI, with bilateral thalamic lesions being consistently observed. Symmetric lesions may also be found in the periventricular white matter, internal capsule, putamen, upper brainstem tegmentum, and cerebellum and increased serum transaminase levels without elevation in serum ammonia levels.

Exclusion of other diseases

Severe infections, fulminant hepatitis, toxic shock syndrome, haemolytic uremic syndrome, Reye syndrome, and haemorrhagic shock and encephalopathy syndrome are some of the conditions that may present with similar imaging findings to ANE, although ANE is characterised by bilateral symmetric thalamic lesions. In addition, ANE needs to be distinguished from mitochondrial and inherited metabolic disorders, such as Leigh encephalopathy, glutaric acidemia, methylmalonic acidemia, infantile bilateral striatal necrosis, Wernicke encephalopathy, carbon monoxide poisoning, acute disseminated encephalomyelitis (ADEM), acute haemorrhagic leukoencephalopathy, arterial and venous infarction, hypoxia and traumatic head injury.

Table 2: Diagnostic criteria of sporadic ANE as suggested by Mizuguchi include.

1. Acute encephalopathy related to a febrile viral infection: Rapid reduction of consciousness and seizures.
2. Cerebrospinal fluid examination shows normal cell counts and increased protein concentration.
3. Symmetrical and multiple brain lesions on head CT and/or MRI. Bilateral thalamic lesions are always observed. Lesions are often found also in periventricular white matter, internal capsule, putamen, upper brainstem tegmentum and cerebellum. No lesions in the other areas.
4. Elevated serum transaminase levels with no elevation in serum ammonia levels.
5. Exclusion of other diseases (refer text)

ANE: Acute necrotising encephalopathy, MRI: Magnetic resonance imaging, CT: Computed tomography

In cases of familial ANE, also known as ANE1 according to Neilson *et al*.,[16] there is a familial history of neurological symptoms, which might be parainfectious or recurrent encephalopathy following fever, along with additional MRI changes involving one of the following: medial temporal lobes, insular cortices, claustrum, external capsule, amygdala, hippocampi, mammillary and spinal cord.

ANE radiology

In addition, to diffuse brain oedema, there are bilateral symmetric, oedematous/necrotic lesions in specific brain regions, esp. the thalami. The classical neuroimaging of ANE has a concentric structure.[2,8] This typical manifestation is more obvious on ADC of MRI where the centre of the lesion presents a slightly high signal with a low signal in the surrounding of the lesion(cytotoxic oedema) and again high signal in its periphery (vasogenic oedema). DWI shows increased diffusion (necrosis and perivascular haemorrhage) in the centre of the thalamic lesion, restricted diffusion in the surrounding zone, and increased diffusion in the periphery [Figure 1]. Thalamic lesions show hypodensities on CT. In the acute stage, the lesions show low T1, high T2 intensity, and decreased diffusion. In the early subacute stage, the thalamic lesions are concentric due to central T1 hyperintensity indicating haemorrhagic changes.[1] In the late subacute stage, there is progressive cerebral atrophy, and shrinkage or disappearance of thalamic lesions. Gadolinium-contrast MRI has been reported to identify lesions at an early stage of ANE (alteration of the BBB permeability) when conventional CT, MRI, and even DWI and ADC may show no abnormalities.[2] The gadolinium-contrast MRI may, therefore, help in early diagnosis and enable the initiation of prompt treatment to alleviate neurological sequelae in ANE. However, enhancement on gadolinium-contrast MRI is not always seen; therefore, this needs to be interpreted with caution. Magnetic resonance spectroscopy (MRS) may provide additional information, though it may not be consistent or specific. Transient lipid-lactate complex peak and glutamate/glutamine complex peak on MRS have been reported in patients with ANE. The glutamate/glutamine complex peak on MRS might depend on the severity of the disease.[2] Spinal cord involvement may occasionally be noted. The hippocampus/amygdala is more often involved in familial ANEC.

Other than ANE, conditions like ADEM and AE with biphasic seizures and late reduced diffusion (AESD) may also exhibit thalamic lesions. In addition, symmetrical brain lesions may be observed in the cerebral and/or cerebellar white matter

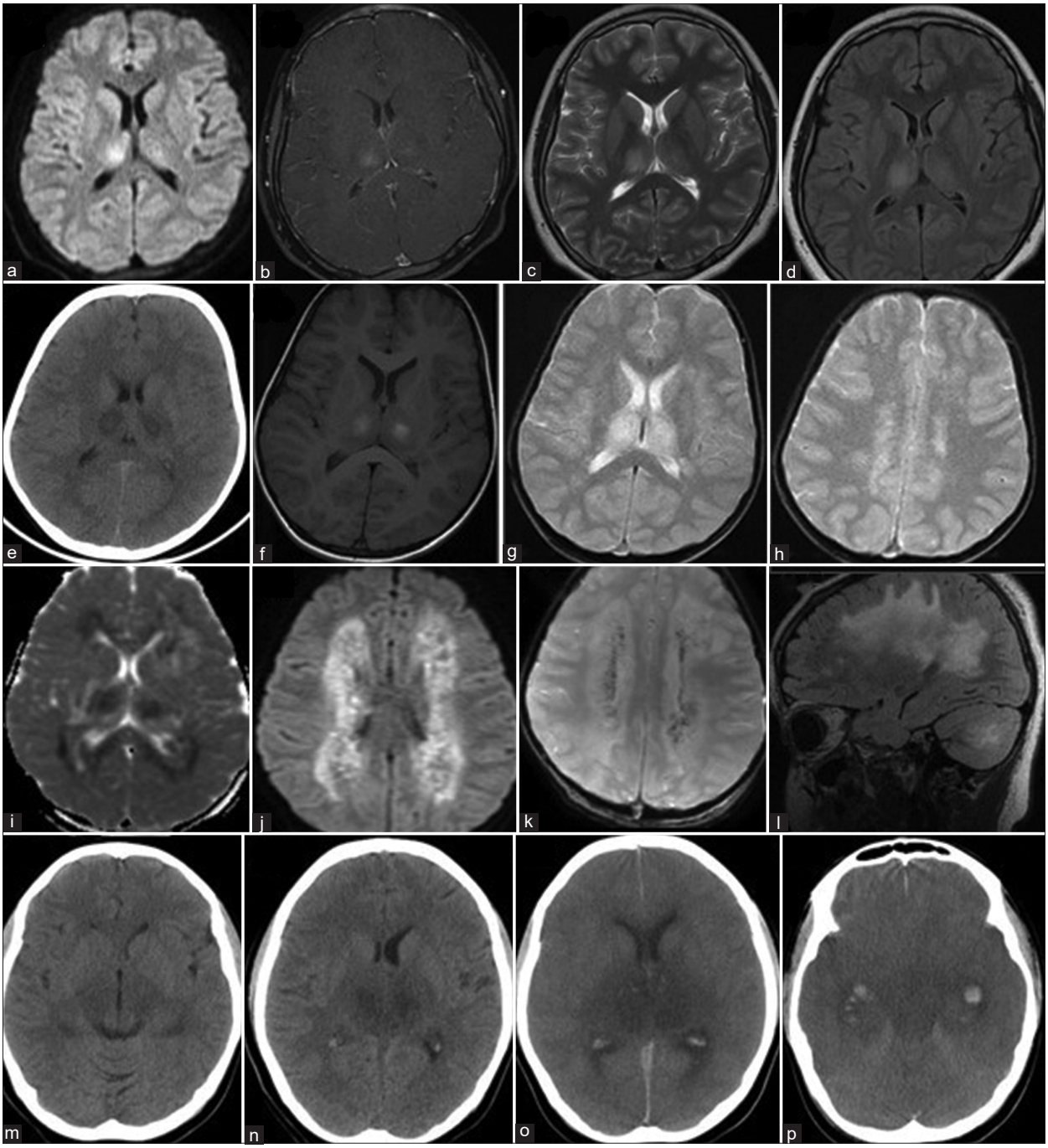

Figure 1: (a) Axial diffusion-weighted image shows restricted diffusion in bilateral thalami. (b) Axial T1 post-contrast image shows enhancement in thalami R>L. (c and d) Axial T2-weighted and T2 fluid-attenuated inversion recovery images show hyperintensities in bilateral thalami from a child with good recovery without any deficits. (e) Axial image of non-contrast computed tomography head shows bilateral thalamic hypodensities. (f) Axial T1-weighted image shows thalamic hyperintensities. (g and h) Axial gradient echo image shows hyperintensities in bilateral thalami and deep white matter in a child with mild to moderate disability-learning disability, squint, epilepsy. (i) Axial apparent diffusion coefficient maps suggest restricted diffusion in bilateral thalami and periventricular white matter. (j) Axial diffusion-weighted restricted diffusion in bilateral deep white matter. (k) Axial susceptibility-weighted images suggest haemorrhage in the central part of bilateral deep white matter lesions. (l) Sagittal T2-weighted image shows hyperintensities in cerebral and cerebellar white matter from a child with severe disability-wheel chair bound. (m and n) Axial non-contrast computed tomography (CT) head shows hypodensities in midbrain, subthalamic nucleus and bilateral thalami at admission. (o and p) Axial non-contrast CT head a day later shows hypodensities in thalami with effacement of sulcal spaces, blurring of grey-white junction and intraventricular bleed in a child who succumbed to acute necrotising encephalopathy of childhood.

and brain stem tegmentum in ANE. Unlike ADEM, the white matter lesions in ANE are generally located in the internal capsule and deep white matter and are not asymmetric. Furthermore, ANE does not involve the subcortical white matter, as seen in AESD (bright tree appearance).

Laboratory findings

Laboratory findings may vary between patients, while some could be used to support the diagnosis of ANE, such as abnormalities of liver function without hyperammonemia.[4] Increased protein levels of CSF and low platelet count could be a predictor of the prognosis of the disease. The protein levels in CSF are elevated in two-thirds of patients, possibly due to the extravasated plasma proteins and the disintegrated neural proteins (myelin basic protein).[2]

Treatment

There have been limited reports on specific treatments for ANE. In a retrospective study conducted in Japan, corticosteroids (such as pulsed steroid therapy or intravenous dexamethasone) administered within 24 h after symptom onset were associated with better outcomes in ANE patients without brainstem lesions.[17] Although there is insufficient evidence for its use in ANE, early pulse steroid therapy is recommended shortly after symptom onset.[1] The role of intravenous immunoglobulin has not been conclusively proven, and while some authors have reported good outcomes with plasmapheresis, further research is needed. Therapeutic hypothermia, utilised as an anti-cytokine therapy, may hold the potential to improve outcomes in children with ANE, particularly if initiated within 12 h after onset.[2] There have also been anecdotal reports of successful use of tocilizumab.[18]

Presently, effective treatment for ANE has not been firmly established, but early pulse steroid therapy is recommended. The efficacy of intravenous immunoglobulin or hypothermia in treating ANE remains unproven.[1] The management of ANE faces challenges due to the lack of a standardised treatment protocol, the need for intensive care during the acute phase and the requirement for rehabilitation services during the post-hospitalisation phase, with outcomes varying among individuals.

Outcome and prognosis

Outcomes in ANE are potentially devastating but variable.[19,20] The ANE Severity Score (ANE-SS) is determined by considering clinical and laboratory parameters, which include the presence of shock (3 points), brain stem lesions or age over 48 months (2 points each), and platelet count <100,000/uL or CSF protein above 60 mg/dL (1 point each).[21] The total score can range from 0 to 9 points, and patients are categorised into low-risk (ANE-SS 0–1 points), medium-risk (ANE-SS 2–4 points) or high-risk (ANE-SS 5–9 points) groups. High-risk ANE-SS has been associated with increased mortality and severe morbidity. Wong *et al.* devised an MRI scoring system that considers the presence of haemorrhage, cavitation and lesion location (brain stem and/or white matter – cerebral, cerebellar, or both).[22] One point is assigned for each of these features, and the composite score correlates with neurological outcomes. Serial disability scoring is valuable for assessing the progress of ANEC patients during follow-up, and evaluation at one month after diagnosis can aid in predicting long-term outcomes.[19]

Continued neurologic recovery at follow-up has been described.[9,19] Although patients with ANE may eventually have a good outcome, the recovery is gradual; hence, at discharge, many children may have significant neurologic problems. The reason for the good outcome in some reports may be, firstly, due to increased recognition of the mild form based on the clinical symptoms and radiologic findings and secondly, to prompt and appropriate treatment after early diagnosis of the disease.

Future directions

ANEC is a relatively uncommon but important cause of acute febrile encephalopathy with diagnostic neuroimaging findings. Increasing awareness about ANE is needed to promote early diagnosis and enable appropriate treatment. On 31 July, ANE awareness day can be utilised by running educational campaigns about the disease. Standard institutional protocols will facilitate timely treatment. Multicentre studies are needed to establish the role of immunotherapy, including steroids and hypothermia, in improving outcomes in this ANE. Rehabilitation needs to be emphasised as these children tend to recover gradually.

CONCLUSION

Infection-associated ANEs remain under-recognised and pose a challenge in neurocritical care. The judicious use of neuroimaging and laboratory tests helps in diagnosing distinct clinicoradiologic AE syndromes. ANE should be suspected if fever (especially from a viral illness) is followed by rapidly progressing altered sensorium, tone abnormalities, or seizures. Neuroimaging typically shows symmetric lesions in the thalami, bilateral lesions in the internal capsule, cerebellar white matter, and brainstem tegmentum. Although evidence-based treatment guidelines are lacking, standard supportive care, immunotherapy (high-dose pulse methylprednisolone), therapeutic hypothermia within 12 h (to decrease cytokines), and anti-oedema measures may be beneficial. Outcomes in ANE are heterogeneous, with high mortality and neurodeficits in survivors. Predictors of outcome include, younger age, increased CSF protein/transaminases, presence of haemorrhagic/necrotic/brainstem lesions on neuroimaging and ANE-SS'.

Clinical significance

Infection-associated AE syndromes are an important cause of AE. Recognition of specific syndromes is crucial for management. Among them, 'ANE has distinctive neuroimaging findings that can aid in the early diagnosis and prompt administration of specific treatment to improve outcomes'.

Ethical approval

The research/study complied with the Helsinki declaration of 1964.

Declaration of patient consent

Patient consent was not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Mizuguchi M, Ichiyama T, Imataka G, Okumura A, Goto T, Sakuma H, *et al.* Guidelines for the diagnosis and treatment of acute encephalopathy in childhood. Brain Dev 2021;43:2-31.
2. Wu X, Wu W, Pan W, Wu L, Liu K, Zhang HL. Acute necrotizing encephalopathy: An underrecognized clinicoradiologic disorder. Mediators Inflamm 2015;2015:792578.
3. Mizuguchi M, Abe J, Mikkaichi K, Noma S, Yoshida K, Yamanaka T, *et al.* Acute necrotising encephalopathy of childhood: A new syndrome presenting with multifocal, symmetric brain lesions. J Neurol Neurosurg Psychiatry 1995;58:555-61.
4. Mizuguchi M. Acute necrotizing encephalopathy of childhood: A novel form of acute encephalopathy prevalent in Japan and Taiwan. Brain Dev 1997;19:81-92.
5. 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.
6. Yadav S, Das CJ, Kumar V, Lodha R. Acute necrotizing encephalopathy. Indian J Pediatr 2010;77:307-9.
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.
8. Yoganathan S, Sudhakar SV, James EJ, Thomas MM. Acute necrotising encephalopathy in a child with H1N1 influenza infection: A clinicoradiological diagnosis and follow-up. BMJ Case Rep 2016;2016:bcr2015213429.
9. Gupta S, Banerjee B, Sasidharan SK, Acharya UV. Clinical, laboratory, radiologic profile, and outcome in acute necrotizing encephalopathy of childhood (ANEC)-a case series. J Pediatr Crit Care 2021;8:192-6.
10. Carod-Artal FJ, Wichmann O, Farrar J, Gascón J. Neurological complications of dengue virus infection. Lancet Neurol 2013;12:906-19.
11. 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.
12. Poojari VS, Shah I, Shetty NS. Acute necrotising encephalopathy of childhood secondary to rotaviral diarrhoea. Indian Pediatr 2021;58:491.
13. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. Radiology 2020;296:201187.
14. Okumura A, Abe S, Kidokoro H, Mizuguchi M. Acute necrotizing encephalopathy: A comparison between influenza and non-influenza cases. Microbiol Immunol 2009;53:277-80.
15. Neilson DE, Adams MD, Orr CM, Schelling DK, Eiben RM, Kerr DS, *et al.* Infection-triggered familial or recurrent cases of acute necrotizing encephalopathy caused by mutations in a component of the nuclear pore, RANBP2. Am J Hum Genet 2009;84:44-51.
16. Neilson DE, Eiben RM, Waniewski S, Hoppel CL, Varnes ME, Bangert BA, *et al.* Autosomal dominant acute necrotizing encephalopathy. Neurology 2003;61:226-30.
17. 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.
18. Koh JC, Murugasu A, Krishnappa J, Thomas T. Favorable outcomes with early interleukin 6 receptor blockade in severe acute necrotizing encephalopathy of childhood. Pediatr Neurol 2019;98:80-4.
19. Lim HY, Ho VP, Lim TC, Thomas T, Chan DW. Serial outcomes in acute necrotising encephalopathy of childhood: A medium and long term study. Brain Dev 2016;38:928-36.
20. Lee YJ, Hwang SK, Kwon S. Acute necrotizing encephalopathy in children: A long way to go. J Korean Med Sci 2019;34:e143.
21. Yamamoto H, Okumura A, Natsume J, Kojima S, Mizuguchi M. A severity score for acute necrotizing encephalopathy. Brain Dev 2015;37:322-7.
22. 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.

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