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CASE REPORT

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Acute necrotizing encephalopathy of childhood from Eastern Africa

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Key Clinical Message: Acute necrotizing encephalopathy leads to devastating neurological sequelae and even death. Clinician should try not to miss this diagnosis especially in the pediatrics whenever there are neurological symptoms due to viral infection.

Abstract: Acute necrotizing encephalopathy (ANE) is a rare disease affecting the central nervous system. It leads to devastating neurological sequelae with a mortality rate of approximately 30%. Clinicians should have high suspicion whenever there is neurologic deficit and history of viral infections especially involving upper respiratory tract in the pediatric age group.

KEYWORDS
encephalopathy, immunoglobulin, necrotizing, pediatrics

1 | INTRODUCTION

Acute necrotizing encephalopathy (ANE) is a rare cause of acute encephalopathy, which was first described in 1995 by *Mizuguchi* et al whereby it was thought to affect population of Eastern Asia particularly children.[1] The condition affects the central nervous system and is characterized by altered level of consciousness usually accompanied with seizures. *Mizuguchi* et al proposed the criteria for diagnosis, encephalitis preceded by viral infections accompanied with altered level of consciousness, absent of pleocytosis in cerebral spinal fluid analysis, elevated aminotransferase levels, exclusion of other diseases presenting with similar clinical presentations, and lastly the radiological hallmark features consisting of symmetrical bilateral brain lesions affecting the thalami, upper tegmentum, putamen, periventricular white matter, and cerebellum.[1–3] After the advancement of imaging modalities such as magnetic resonance imaging (MRI), sporadic cases have been reported to occur elsewhere especially in the western countries.[2] As per the previous reports, this condition predominantly affects not only children but also adolescents and, in a few cases, the adult population.[3] We report a case of acute necrotizing encephalopathy of childhood from Tanzania treated with a good outcome.

2 | CASE PRESENTATION

A 9-year-old male patient of African descent was seen at our emergency department (ED) with a three-day history of inability to speak. The informant was his father who reported that his son's symptoms started suddenly, which were accompanied by decreased level of consciousness and excessive sleepiness over the period. Prior to the

aforementioned symptoms, the patient had severe headache, which he reported to be excruciating to the point that the child was crying all the time. At the beginning of his illness, he was taken to the nearby clinic whereby he was prescribed analgesics and antibiotics for presumptive upper respiratory tract infections since the child had features suggestive of tonsillitis.

On examination at our ED, the child was well-nourished boy but ill looking, semiconscious with Glasgow coma score (GCS) E4V1M5 = 10. He had nasogastric tube (NGT) in-situ. His airway was patent and protected. His pupils were equally reactive to light, motor function on both the upper and lower limbs power were 3/5 and 2/5, respectively. The patient had opisthotonos posture with positive Kernig's sign, which initially made us think of meningitis. Due to the patient's decreased level of consciousness, assessing all cranial nerves was not easy. However, at least he had a normal gag reflex that he could protect his airway. His hematological and biochemistry laboratory investigations were unremarkable including procalcitonin level, except for the raised serum transaminases ALT 56.3 (1–50 U/L) and AST 139.2 (1–50 U/L). He was also screened for dengue, malaria, SARS-CoV-2, and HIV, which were all negative. Other viral serology tests were unavailable at our center. Lumbar puncture was not performed due to evidence of cerebral edema in brain computed tomography (CT) scan (Figure 1). The patient was then given hypertonic saline 150 mL of 3% sodium chloride, antibiotics, and antiviral as empirical treatment for meningitis.

Despite the initial therapy until the third day, the patient's condition was not improving; hence, a brain MRI was performed which showed bilateral thalami involvement with hyperintensity on flair images with central hemorrhagic transformation. The putamen and central white matter showed restricted diffusion (Figure 2). Based on these findings, a new diagnosis of ANE was made. Thus, the decision of administering intravenous immunoglobulin (IVIG) was sought, and he was given 25 g (dose of 1 g/kg) as a single dose. After 7 days of treatment, the patient's GCS improved, and later he was discharged through physiotherapy clinic. The patient was seen after 2 weeks at our hospital clinic as a follow-up. There was a remarkable improvement in his motor function as he was able to walk on his own without any support. He was well coherent with the conversation except for his slurred speech; otherwise, all other cranial nerves were intact.

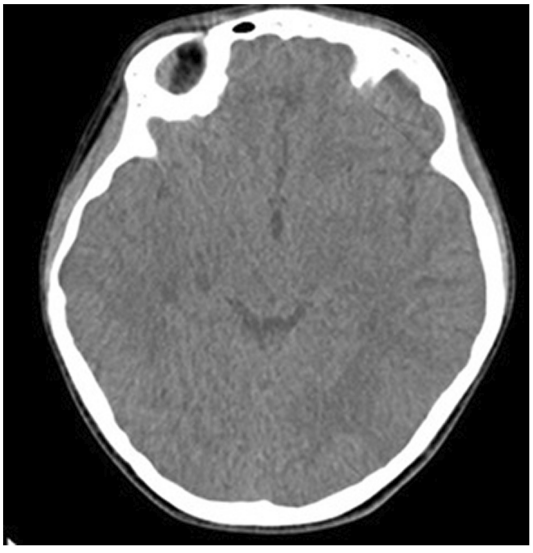

FIGURE 1 CT scan image showing evidence of cerebral edema.

3 | DISCUSSION

Acute necrotizing encephalopathy (ANE) of childhood is a rare form of encephalopathy, and its etiology is yet unknown. It is often associated with viral infections such as influenza A and B, parainfluenza, and human herpes virus-6 (HSV-6).[4] There are few cases being reported in adult population especially in western countries although most of the cases affect children and adolescents, in which majority of them are seen to be of Asian origin.[2,5]

The main pathogenesis of the disease remains unknown despite varying hypothesis such as the autoimmune response inducing cytokine storm that later leads to neurovascular damage[6] as well as geographical location whereby Eastern Asian countries have genetic predisposition for region-specific pathogens causing ANE.[7]

Acute necrotizing encephalopathy presents like any other forms of encephalopathy with nonspecific prodromal symptoms including fever, cough, and gastrointestinal disturbances. As the disease progresses, in few days, life-threatening symptoms occur including seizures, ataxia, and coma.[6] Reports from Eastern Asian countries showed the affected ages are usually between 6 and 18 months old, which accounts 50% of cases.[2] The onset of neurological dysfunction usually occurs from 12 to 72 h after the onset in which 40% of the cases present with seizures.[2] A review made more recently by *Yuan* et al.[8] showed that 94% of the cases have early seizure activity most frequently being persistent tonic–clonic in nature. In our case, the patient presented with altered level of consciousness for the past 3 days, aphasia and excessive drowsiness. The symptoms were preceded by headache, but no seizures were reported.

The diagnosis of ANE significantly depends on the radiological hallmark with symmetrical lesions involving thalami, tegmentum of upper thalami, and other regions of the brain such as the white matter, basal ganglia, brain stem, and cerebellum.[9] The laboratory findings are not specific for the diagnosis as they are mainly supportive and most cases

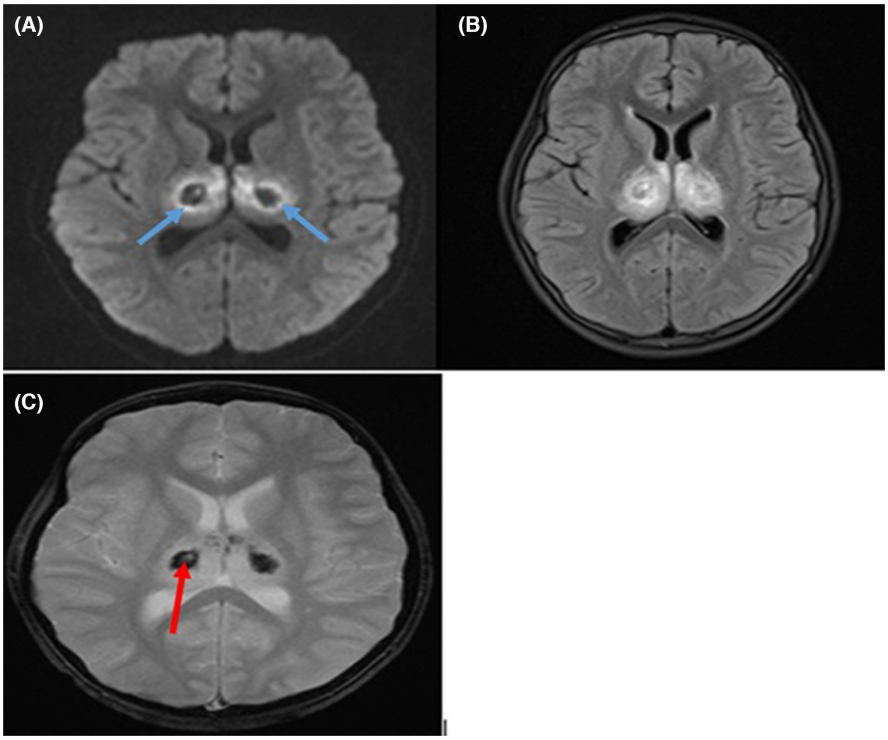

FIGURE 2 MRI Image (A) showing bilateral thalamic and putamen involvement with restricted diffusion (blue arrows) (B) shows flair image showing bilateral thalamus hyperintensity. (C) is the T2 heme axial sequence showing hemorrhagic transformation (red arrow).

present with elevated white blood cell counts, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).[10] Serum transaminase, lactate dehydrogenase (LDH), and creatinine kinase (CK) are frequently observed to be elevated as there is direct relation to increased fibrin degradation products.[8] Occurrence of electrolyte imbalance is uncommon. Cerebral spinal fluid (CSF) analysis, though it accounts to be nonspecific in most cases, has been observed to have raised protein concentration.[2,8] We excluded other differentials including Reye's syndrome, which mostly mimics ANE in which the prior patients are exposed to salicylate therapy and usually presents with features of hypoglycemia and lactic acidosis in which our patient did not have.

Most of the reported causes of acute necrotizing encephalopathy are caused by viral infections such as influenza, HSV-6, parainfluenza, and other related viral infections such as dengue virus; hence, it is important also to do the serology to understand the causative agent, which may be of benefit in the treatment and outcome. In our case from the history and clinical presentation of the patient, meningitis was the main provisional diagnosis, and then later ANE was added into our diagnosis list. Viral infections cause cytokine activation, which leads to the trigger of coagulation cascade.[1] It is seen that chronic viral infections are associated with thrombotic complications while acute infections may cause both thrombosis and hemorrhagic complications,[11] as in our case with evidence of hemorrhagic transformation in the thalamic region. The working diagnosis changed when MRI brain was done as the patient's condition was not improving, and this is when acute necrotizing encephalopathy as an incidental finding was noted. The laboratory findings were not alarming for any central nervous system infection except for elevated transaminase level, which is usually noted in acute necrotizing encephalopathy. Lumbar puncture was contraindicated due to the presence of cerebral edema.

Currently, there is no consensus on the treatment for acute necrotizing encephalopathy. Treatment is mainly based on a symptomatic approach, which includes the use of empirical antiviral treatment.[12] Depending on the patient's clinical condition, intensive care admission may be required such as in cases with active convulsions or other life-threatening conditions such as septic shock. Most of the literature recommend the use of intravenous glucocorticoids and immunoglobulins as it has been seen to improve the patient's clinical condition remarkably.[6,10] In our patient, a combination of intravenous immunoglobulin, antiviral medications together with antibiotics was empirically prescribed medications during his hospital stay. Although immunoglobulin injection was not initiated early, its efficacy in this case cannot be predicted.

The outcome of ANE of childhood is generally poor. The mortality rate has been reported to be 30%. The survivors may be subjected to serious neurological complications such as muscle spasticity and speech disorders, but less than 10% of cases have recovered without any neurological sequelae.[8] Abnormal laboratory investigation with significant elevated levels of serum aminotransferase and CSF protein makes the prognosis of the disease to be worse.[10] With the aid of physiotherapy, our patient could

walk on his own in contrast to his initial presentation of being bedbound with limited neuromotor activities on his both upper and lower limbs.

4 | CONCLUSION

To the best of our knowledge, there have not been any similar cases reported of ANE of childhood in Tanzania. Due to its rarity, a delay in establishing diagnosis can lead to poor patient outcomes. Our emphasis is to always maintain a high level of suspicion in similar clinical presentations to ensure ANE does not go unrecognized.

AUTHOR CONTRIBUTIONS

Hilary Chipongo: Data curation; writing – original draft. **Shaffin Rajan:** Writing – review and editing. **Abizer Sarkar:** Investigation; resources; visualization. **Ronald McLarty:** Writing – review and editing. **Esmail Sangey:** Supervision; writing – review and editing.

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None.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Authorea at https://doi.org/10.22541/au.167965226.68433329/v1.

CONSENT

Informed and written consent was obtained from the patient to publish in this case report.

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