Acute Necrotizing Encephalopathy of Childhood: A Case Report

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ABSTRACT

Acute necrotizing encephalopathy of childhood is uncommon, rare, and fatal encephalopathy, which usually occurs after respiratory or gastrointestinal infections. The disease was first described in Japan by Mizughuchi in the year 1995 (1). The characteristic clinical and magnetic resonance imaging brain findings were noticed in the index child following human herpes virus-6 viral infection. A number of metabolic encephalopathies and other para-infectious conditions have to be excluded to make the final diagnosis. It carries poor prognosis, but our child recovered well after early steroid therapy.

Key words: *Acute necrotizing encephalopathy of childhood, Early steroid therapy, Human herpes virus-6*

Acute necrotizing encephalopathy of childhood (ANEC) is a rare, severe atypical encephalopathy of para infectious etiology usually triggered by viral infections and is associated with rapid deterioration of sensorium and seizures [1]. It was first described by Mizuguchi from Japan in 1995 [1]. It is seen predominantly in previously healthy young children or infants of East Asian countries such as Japan and Taiwan. However, sporadic cases of this illness have been reported from all around the globe [1,2]. Influenza virus, human herpes virus 6 (HHV-6), herpes simplex virus, mycoplasma, and dengue viruses are among the most common infections causing ANEC [3-5].

Recently, acute hemorrhagic necrotizing encephalitis was observed in a young adult due to coronavirus disease-19 infection [6]. The elevation of hepatic enzymes is unique without hyperammonemia [7]. A recurrent or familial form is associated with mutations in the RANBP2 gene and is noted as ANE1 [7,8]. Classical magnetic resonance imaging (MRI) findings include multifocal symmetrical lesions in thalami, brainstem, and cerebellum [3,9]. The physicians should rule out other causes of encephalopathies such as fulminant hepatitis, Reye's syndrome, toxic shock syndrome, Leigh encephalopathy, organic academia, hypoxic brain insult, acute disseminated encephalomyelitis, venous and arterial infarcts in children, and occasionally heatstroke [10]. The prognosis is poor in most cases. We report a case of ANEC following HHV-6 infection in a previously healthy 9-month-old infant.

CASE REPORT

A previously healthy 9-month-old female infant presented to us with fever for 4 days, loose stools for 2 days, and decreased activity for 1 day. At the time of admission, she was irritable, drowsy and her deep tendon reflexes were brisk with the Glasgow Coma Scale of 13/15. Her pupils were equal and reacting to direct light and the hydration status of the child was good. However, after 1 h of admission in the pediatric intensive care unit (PICU), she developed right-sided focal seizure, which was aborted with short-acting benzodiazepine injection midazolam, and later, she was loaded with inj. levetiracetam 20 mg/kg IV route over 20 min. The seizure got controlled but encephalopathy with signs of meningitis (neck stiffness, Kernig's sign, and Brudzinski signs) persisted. Hence, an initial provisional diagnosis of acute meningoencephalitis was made. Other differential diagnoses kept in mind were metabolic encephalopathy with sepsis, hypoxic-ischemic encephalopathy (HIE) due to status epilepticus, and Reye's syndrome, respectively.

She was given O_2 therapy, intravenous (IV) fluids, IV third-generation cephalosporins, and IV acyclovir initially for 5 days. After stabilizing the airway, breathing, circulation, and neurological status of the child, a lumbar puncture was done after ruling out optic disc edema by fundoscopy. The cerebrospinal fluid (CSF) report revealed total two cells with 100% lymphocytes, CSF glucose was 38 mg/dl, and CSF total protein was 44 mg/dl. Thus, there was neither CSF pleocytosis nor an increase in CSF protein.

On the next day of admission, she again had two episodes of seizures in the form of generalized tonic-clonic seizures, which were controlled with inj. midazolam and also loaded with inj. fosphenytoin sodium, and meanwhile, the dose of inj. levetiracetam was increased to 60 mg/kg/day. Her complete blood count report showed hemoglobin of 9.4 g/dl, white blood cells of 13,500/mm^3, and platelet count of 176,000/mm^3. The liver function tests showed total serum bilirubin of 1 mg%, direct – 0.2 mg%, serum glutamic oxaloacetic transaminase – 96, serum

glutamic-pyruvate transaminase – 92, alkaline phosphatase 47, proteins 5.3 g%, and albumin 2.8 g%. The coagulation profile was within the normal range.

The serum sodium (Na) was 139 meq/l, potassium (K^+) 4.2 meq/l, chloride 99 meq/l, and serum creatinine 0.6 mg%. The random blood sugar was 124 mg/dl. The venous blood gas of the child revealed pH of 7.38, partial pressure of carbon dioxide ($PaCO_2$) of 39 mmHg, partial pressure of oxygen (PaO_2) of 39.5 mmHg, bicarbonate concentration HCO_3 – 22.8 meq/l, blood and extracellular fluid base excess BE – 1.8, serum lactate 2.1, and serum ammonia was 32 µmol/l. Her nasopharyngeal swab for H1N1 was negative and her blood culture was also negative.

MRI brain was done on the 2nd day of hospitalization but within 24 h of admission, revealed hyperintensity lesions in bilateral thalami, bilateral peritrigonal region, and bilateral cerebellar white matter with normal MR venography. Her electroencephalogram was suggestive of focal epileptiform wave discharges over the left frontal and right temporal region. The workup for inborn errors of metabolism (IEM) such as urine gas chromatography–mass spectrometry (GC–MS) for organic acids and blood sample for Tandem mass spectroscopy for serum amino acids profile and Acyl carnitine profile came negative after 1 week. CSF sample for polymerase chain reaction (PCR)-based viral panel confirmed HHV-6 triggered ANEC, whereas PCR-based test for HSV1 and HSV2 was negative.

The patient was started with pulse dose methylprednisolone (30 mg/kg/day) within 24 h of admission, which was continued for a total of 3 days, and later, oral tapering dose was continued for 2 weeks. IV acyclovir was stopped after the HHV-6-positive report in the CSF. She was started with IV valganciclovir for 1 week followed by enteral dose for a total of 21 days. She was treated with anti-edema measures (IV 3% saline bolus of 5 ml/kg followed by infusion at 0.5 ml/kg/h) for 4 days and antiepileptic drug (levetiracetam). Fosphenytoin sodium was tapered and stopped within 5 days. She initially had spasticity and dystonia in all four limbs requiring anti-spasticity medications in the form of low-dose oral diazepam (1 mg 12 hourly), trihexyphenidyl (1 mg 12 hourly), and baclofen sodium (2 mg 12 hourly), physiotherapy, and nursing care like nasogastric tube feeding.

After 10 days of the hospitalization in PICU, her sensorium improved and started interacting with parents. She gained back the social smile and her limb spasticity disappeared. She started oral feeding and so she was transferred to the pediatric general ward for 4 days and later discharged home. On discharge, she was continued oral valganciclovir, oral levetiracetam, and low-dose baclofen sodium (2.5 mg 12 hourly). Pediatric neurologists and physiotherapists were part of the management. After 2 weeks and 6 months follow-up in the outpatient department (OPD), she was able to walk, babble, and no new neurological deficit was observed.

DISCUSSION

ANEC is a clinical and neuroradiologic entity. The exact etiopathogenesis is not known. Influenza A virus, mycoplasma, herpes simplex virus, and HHV-6 have been reported as common causative agents, directly, or through an immune-mediated mechanism [1-3]. Most cases of ANEC are sporadic and commonly follow respiratory or gastrointestinal illness [2]. In the index case, a 9-month-old child had presented with a history of fever, loose stools, and decreased activity within 3–4 days of onset of illness which is similar to a study done by Skelton *et al*. [3].

The IEM workup including blood samples for TMS to assess serum amino acids and acylcarnitine profile and urine for GC–MS to look for organic acids profile was normal without metabolic acidosis and ruled out metabolic encephalopathies such as organic academia and Leigh's encephalopathy. There was no history of administration of aspirin therapy for the current illness and no rapid onset fulminant hepatic failure precluding Rey's syndrome. The hallmark of HIE in neuroimaging includes cortical and subcortical white matter involvement along with basal ganglia affection, especially parasagittal white matter, putamen nucleus which was absent here, hence ruling out HIE. The mildly elevated liver enzymes with normal coagulation profile excluded fulminant hepatic failure.

The normal MR venography without dehydration clinically exempted cerebral sinus venous thrombosis. Hence, the diagnosis of ANEC was made with characteristic clinical and neurodiagnostic findings in this child. The characteristic clinical history and MRI findings with the absence of CSF pleocytosis are diagnostic features of ANEC [7]. It is believed that some viruses or its variant cause the rapid development of intracranial cytokine formation which causes blood–brain barrier damage in particular regions of the brain resulting in localized edema, congestion, and hemorrhage, without any signs of direct viral invasion or post-infectious demyelination [1,2,11,12].

The classical MRI Brain findings (Fig. 1) in the child like multifocal, bilateral symmetric brain lesions affecting the bilateral thalamic areas, brainstem tegmentum, or cerebellar medulla, cerebral periventricular white matter is comparable to the previous studies by Salehi *et al*., Abbas *et al*., Hoshio *et al*., and Hassanzadeh Rad and Aminzadeh [12-15]. According to Okumura *et al*, the localized edema, congestion, or hemorrhage were more severe in the center of thalamus than periphery giving the concentric appearance on imaging [16].

The clinical course of ANEC is fulminant and diverse, from mild with complete recovery to severe form with high mortality [1,16]. The current study showing the absence of CSF pleocytosis or increase in CSF proteins is comparable to the study done by Hassanzadeh Rad and Aminzadeh [15]. The child had typical clinical, neuroradiological findings without any family history of similar episodes which ruled out the familial or genetic type of ANEC so genetic workup was not done in this child. The study done by Ahmadabadi *et al*. observed an epidemic of three cases in the same family in Iran with typical presentations [17].

The treatment of ANEC due to HHV-6 in immunocompetent children is symptomatic, i.e., control of seizures, treatment of raised ICP, and temperature control and early steroid therapy. However, the basic intensive care support of airway, breathing,

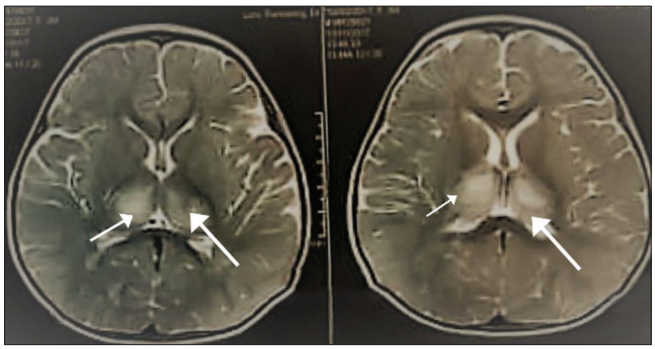

Figure 1: MRI Brain (T2W Axial image) showed bilateral symmetrical signals with enlargement of thalami

circulation, and disability is needed in all sick children. Okumura *et al*. observed that steroid therapy within 24 h of the onset of the disease carries a better prognosis of children with ANEC without brainstem involvement [16]. The multiple small studies have shown some improvement with valganciclovir therapy and centers for disease control and prevention recommends trial therapy with either foscarnet, valganciclovir, or cidofovir in immunodeficient children, especially post-organ transplants and in complicated Human Herpes Virus central nervous system infection [18,19]. In our patient, we gave trial of IV valganciclovir (7 days) with IV pulse dose methylprednisolone (for 3 days) and later both medications were continued orally for 3 weeks. Our child recovered completely without neurological sequelae within 10 days of hospitalization and doing good later on OPD basis follow-up without any neurological deficits.

CONCLUSION

ANEC should be considered in the differential diagnosis of a child presenting with febrile encephalopathy with seizure. Presentation in ANEC can vary from mild to a severe fatal form. Early steroid therapy as an immunomodulatory drug and specific antiviral therapy may be helpful and can modify the disease outcome.

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