Acute Necrotizing Encephalopathy

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ABSTRACT

Objective: To describe the clinical profile of pediatric patients with acute necrotizing encephalopathy (ANE).

Study Design: Case series.

Place and Duration of Study: Aga Khan University Hospital, Karachi, Pakistan, from January 2014 to October 2017.

Methodology: Retrospective review of medical records of all children aged 1 month to 16 years admitted with diagnosis of ANE was done. Diagnosis was based on the criteria of ANE described by Mizuguchi et al. The clinical profile, management and outcome were recorded.

Results: There were 17 patients. The mean age at presentation was 55.47 ± 59.13 months. The most common presentation was fever with altered consciousness and seizures. The mean length of stay was 11.7 ± 5.6 days. Viral etiology was established in three children. The managements of the patients were symptomatic and supportive; the combination of antibiotics, antivirals and anticonvulsants was the most frequently used regimen. Eleven out of seventeen (65%) patients required intensive care unit admission and mechanical ventilation; while others were managed in the special care unit. Three (17.6%) children died during the stay; while 10 (58.8%) children developed severe morbidity in the form of neurodevelopmental sequelae.

Conclusion: The devastating outcome of ANE seemed to occur with increasing severity at the time of initial presentation; and the use of antivirals and immunomodulation did not alter the course of disease.

Key Words: Acute necrotizing encephalopathy (ANE), Encephalopathy, Encephalitis, Neurological sequelae.

INTRODUCTION

Acute necrotizing encephalopathy (ANE) is a distinct clinicoradiologic entity, first described in 1995 by Mizuguchi et al. as a possible cause of acute encephalopathy.1 Majority of the cases have been reported from Asian countries including Japan, Taiwan and Pakistan.2 Recently, a case of ANE has been reported from Karachi, Pakistan caused by dengue fever.3 However, there is emerging literature from other parts of the world.4 ANE often affects infants and toddlers,5 but adolescent and adult cases have also been reported.6,7 Prodromal upper respiratory and gastrointestinal viral symptoms are followed by dramatic neurological deterioration culminating in death or profound neurocognitive morbidity.7

The etiology and pathogenesis of this disease remain largely unknown. Most ANE cases are sporadic and non-recurrent; namely, isolated ANE. Influenza A virus, rubella, coxsackie A9, human herpes virus-6, herpes simplex virus, and mycoplasma have been identified as common causative agents.8 It was assumed to be an immune mediated phenomenon.9 However, recent literature has implicated pro-inflammatory cytokines and the cytokine receptors in the pathophysiology.10 There have been reports that suggest increased genetic susceptibility of ANE and a missense mutation in Ran-binding protein 2 (RANBP2) has been established as a genetic risk factor for ANE.11

The typical findings on magnetic resonance imaging (MRI) include multiple, symmetric lesions in bilateral thalami, basal ganglia, cerebral and cerebellar white matter and brain stem.12 Involvement of internal capsule, posterior putamen, periventricular white matter, the external capsule, claustrum, hippocampus, amygdala, mammillary bodies, medial temporal lobes and cervical spinal cord have also been reported.11 The concentric trilaminar pattern in the bilateral thalami on the diffuse weighted imaging (DWI) and apparent diffusion coefficient (ADC) demonstrate both vasogenic and cytotoxic edema along with central haemorrhage and necrosis.9

The prognosis is poor and only 1/10th of the patients affected had good outcome.13 Patients with better outcomes were those with reversible radiological findings.11 Through this case series, the rationale was to provide insight about the clinical profile and radiological findings of the children affected by this rare yet devastating disease in our setting. The objective of the study was to describe the clinical profile of pediatric patients with ANE in terms of clinical presentation, hospital course, diagnostic work-up including magnetic resonance findings and outcome.

METHODOLOGY

Retrospective review of medical records of all children with ages ranging from 1 month to 16 years admitted at Aga Khan University Hospital, Karachi, with the...
diagnosis of ANE was done from January 2014 to October 2017 after approval from Ethical Review Committee (ERC, 3347-Ped-ERC-14). Case identification was done by reviewing data of patients with the diagnosis of acute necrotising encephalopathy of childhood (ICD-10-CM, diagnostic code: G03-9). Diagnosis was based on the criteria of ANE described by Mizuguchi et al.\(^\text{14}\) as, "acute encephalopathy with rapid conscious deterioration, absence of serum hyper-ammonemia, increase in CSF proteins increased cerebrospinal (CSF) protein without pleocytosis, neuroimaging studies showing symmetrical, multifocal lesions involving the thalami with the clinical absence of other diseases resembling ANE."\(^{14}\)

Patients with acute encephalopathy who had multiple focal lesions on MRI that were symmetrically distributed in the bilateral thalami and other brain regions such as the putamina, cerebral and cerebellar white matter, and brainstem tegmentum were included while individuals with metabolic derangements were excluded. Various MRI sequences including T1-weighted, T2-weighted images and post contrast T1-weighted as well as fluid-attenuated inversion recovery (FLAIR) images, diffusion weighted images (DWI), apparent diffusion coefficient (ADC) and susceptibility weighted imaging (SWI) were carried out in all patients. These were reviewed by a team of neuro-radiologists. Severity of the disease at the time of presentation was assessed by the area of care, \textit{i.e.} mild for general, moderate for special, and severe for intensive care unit (ICU).

The patients also underwent virology studies available in our setup that include cerebrospinal fluid polymerase chain reaction for \textit{Herpes simplex} virus (CSF HSV PCR), nasopharyngeal swab for H1N1 and serology for Japanese B encephalitis. Dengue IgM was performed in one patient based on clinical history. Metabolic work-up including plasma ammonia, plasma lactate, urine for organic acids and plasma for amino acids was carried out in all patients. Data was collected on a structured form which included demographics, initial clinical presentation, history of preceding illness, severity of clinical condition at the time of admission, need of ventilatory support, lab parameters, electroencephalographic and MRI findings. Treatment modalities used along with the day and dose of administration as well as the patient's length of stay and outcome were also documented. The outcomes in the surviving patients were determined using classification by Yamamoto et al.\(^{15}\) where they categorised motor impairment as none, mild (walking with or without support), moderate (sitting with or without support) and severe (unable to sit).\(^{15}\) The outcome assessment was done during follow-ups, which were done within few weeks after discharge.

Data was entered and analysed using Statistical Package for the Social Sciences (SPSS) version 20.0. Results were presented as frequencies with percentages for categorical variables and mean with standard deviation for continuous variables.

**RESULTS**

Seventeen patients were identified with a diagnosis of ANE with mean age of 55.47 ±59.13 months (Range: 6 months to 180 months). Details of the clinical course, and management and outcome for each patient are summarized in Table I. Fifty-nine percent (10/17) of the affected cases were girls. There was no history of recent immunisation or family history of similar illness. None of the patients had prior significant medical or developmental issues. The duration of illness before presentation to our setup of the patients ranged from 1 to 20 days with a mean of 7.11 ±5.53 days. In only two patients (12%), the transaminases were elevated. Elevation of ammonia and lactate levels was not observed in any patient. CSF proteins were elevated in
18% (n=3), while CSF pleocytosis was seen in 12% (n=2) of the children. In 11 patients (64%), immunomodulatory medications were used consisting of either Intravenous Immunoglobulins (IVIG, 47%, n=8) or methyl prednisolone pulse dose (12%, n=2) or both (6%, n=1). Antiviral medications including acyclovir and Oseltamivir were used. However, the antiviral drugs were later discontinued in those patients where viral studies revealed no evidence of herpes simplex and H1N1 viral infection. MRI was carried out in those patients, and the findings are listed in Table II. The mean interval between the onset of disease and the initial MR study was 2.53 ±2.4 days, ranging from 1 to 5 days. Only one patient underwent a follow-up MRI which was carried out after 20 days (Figures 1 and 2).

Eleven (65%) children required mechanical ventilation and intensive care unit admission, while others were managed in the special care unit. Three (17.6%) children died during the hospital course. All three of them required admission in PICU at the time of presentation. The mean length of stay was 11.7 ±5.6 days, ranging from 3 to 28 days. All the surviving children were followed in the outpatient department to assess the neurological

Table I: Clinical and MRI characteristics of 17 patients with acute necrotizing encephalopathy (ANE).

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Clinical features</th>
<th>Abnormal investigations</th>
<th>MRI findings</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months/F</td>
<td>Fever, loss of consciousness, seizures</td>
<td>CSF pleocytosis Positive HSV PCR</td>
<td>Bilateral frontal, left parieto-occipital, right occipital lobes, anteromedial portion of both thalami and majority of the corpus callosum</td>
<td>Severe motor impairment, spasticity and seizures</td>
</tr>
<tr>
<td>8 months/F</td>
<td>Fever, loss of consciousness, seizures</td>
<td>None</td>
<td>Bilateral symmetrical, abnormal signals in thalami, basal ganglia and cerebral peduncles</td>
<td>Severe motor impairment, spasticity and seizures</td>
</tr>
<tr>
<td>12 months/F</td>
<td>Fever, loss of consciousness, seizures</td>
<td>Elevated liver enzymes</td>
<td>Bilateral frontal, parietal and occipital lobes, bilateral insular cortex, bilateral basal ganglia and bilateral thalamic regions</td>
<td>Death</td>
</tr>
<tr>
<td>17 months/F</td>
<td>Fever, loss of consciousness, seizures</td>
<td>None</td>
<td>Bilateral symmetrical abnormal T2/FLAIR hyperintense signals with diffusion restriction in periventricular and subcortical deep white matter of bilateral cerebral hemispheres as well as subcortical white matter of cerebellar hemispheres and thalami. Haemorrhage in bilateral thalami</td>
<td>Severe motor impairment and seizures</td>
</tr>
<tr>
<td>17 months/F</td>
<td>Fever, flu like symptoms, right VI cranial nerve palsy</td>
<td>Elevated CSF proteins</td>
<td>Acute infarcts involving bilateral thalami, cerebral peduncle, midbrain and brainstem with central necrosis in bilateral thalami and pons</td>
<td>No sequelae</td>
</tr>
<tr>
<td>19 months/F</td>
<td>Fever, flu like symptoms and seizures</td>
<td>None</td>
<td>Bilateral symmetrical thalami, midbrain and the cerebellum</td>
<td>Severe motor impairment, spasticity and seizures</td>
</tr>
<tr>
<td>23 months/F</td>
<td>Fever, loss of consciousness, seizures</td>
<td>Elevated CSF protein Human Herpes virus-6 in viral panel</td>
<td>Bilateral symmetrical abnormal T2/FLAIR hyperintense signals with diffusion restriction in periventricular and subcortical deep white matter of bilateral cerebral hemispheres subcortical white matter of cerebellar hemispheres and thalami</td>
<td>No sequelae</td>
</tr>
<tr>
<td>2 years/M</td>
<td>Fever, loss of consciousness, seizures</td>
<td>None</td>
<td>Bilateral periventricular region, both thalami, midbrain and medulla</td>
<td>Severe motor impairment, spasticity and seizures</td>
</tr>
<tr>
<td>2 years 6 months/M</td>
<td>Fever, loss of consciousness, seizures</td>
<td>CSF pleocytosis</td>
<td>Abnormal signal intensities in bilateral caudate and lentiform nuclei, bilateral thalami, right insular cortex, right frontal gyr and bilateral temporal lobes</td>
<td>Death</td>
</tr>
<tr>
<td>2 years 7 months/F</td>
<td>Fever, seizures</td>
<td>None</td>
<td>Bilateral thalamic infarcts with diffuse abnormal hyperintense signals involving symmetrically bilateral medial temporal lobes, hippocampi, mid brain and parahippocampal gyrus</td>
<td>Severe motor impairment, spasticity and seizures</td>
</tr>
<tr>
<td>4 years/F</td>
<td>Fever and seizures</td>
<td>Elevated liver enzymes</td>
<td>Abnormal signals are identified in bilateral hippocampi more marked on right side, right insular cortex and bilateral thalami</td>
<td>No sequelae</td>
</tr>
<tr>
<td>4 years/F</td>
<td>Fever, loss of consciousness, seizures</td>
<td>None</td>
<td>T2 hyperintense abnormal signals are identified in bilateral thalami, putamen and insular cortex</td>
<td>Severe motor impairment, spasticity and seizures</td>
</tr>
<tr>
<td>5 years/M</td>
<td>Fever, motor weakness and seizures</td>
<td>Elevated CSF proteins</td>
<td>Symmetrical involvement of the thalamus bilaterally</td>
<td>Severe motor impairment, spasticity and seizures</td>
</tr>
<tr>
<td>7 years/M</td>
<td>Fever and seizures</td>
<td>None</td>
<td>Cortical grey matter, bilateral thalami and left basal ganglia</td>
<td>Severe motor impairment, spasticity and seizures</td>
</tr>
<tr>
<td>14 years/M</td>
<td>Fever, loss of consciousness, seizures</td>
<td>None</td>
<td>Bilateral thalami and midbrain</td>
<td>Severe motor impairment, spasticity and seizures</td>
</tr>
<tr>
<td>15 years/M</td>
<td>Fever and seizures</td>
<td>None</td>
<td>Bilateral thalami and periventricular region</td>
<td>No sequelae</td>
</tr>
<tr>
<td>14 years/F</td>
<td>Fever, seizures and altered sensorium</td>
<td>Dengue IgM positive in serum elevated liver enzymes</td>
<td>Bilateral thalami, midbrain, pons and cerebellar hemisphere</td>
<td>Death</td>
</tr>
</tbody>
</table>
outcome. The mean interval between discharge and first visit was 9 days, ranging from 3 to 30 days. Out of these, 58% (n=10) children who included 8 patients from PICU were found to have severe sequelae. Four (23%) children had no long-term complications.

**DISCUSSION**

In this series, clinical profile and outcome of 17 cases of ANE were described that were managed in the study centre setup. ANE is a rare neurological disease with global involvement of the brain. This disease commonly affects young children and there is no gender predisposition. The male to female ratio in this study was 7:10, while the study by Wong et al. showed a ratio of 2:1. This study demonstrated ANE in adolescents which is an unusual age of presentation. However, several cases have been reported from adult population.\(^\text{7,16,17}\)

Differential diagnoses of ANE include viral encephalitis, hypoxic-ischemic encephalopathy (HIE), Reye's disease, Leigh's disease, acute disseminated encephalomyelitis (ADEM), and acute hemorrhagic leukoencephalitis and Wernicke encephalopathy due to similar clinical, radiological and pathological findings.\(^\text{14}\) Among them, Reye's disease and ADEM are the most difficult to differentiate; especially in patients with elevated transaminases and fatty liver on histopathology.\(^\text{1,18}\) However, Reye's syndrome is differentiated from ANE by certain clinical features and lab parameters. It more commonly affects children below 5 years of age and occurs predominantly in America, Europe and Oceania, being rare in East Asian countries.\(^\text{19}\) In Reye's syndrome, there are metabolic derangements like hypoglycemia, hyperammonemia and lactic acidosis while they are absent in ANE, which was also seen in our patients. Two (12%) of these patients had elevated transaminases; however, studies have shown that transaminases level in ANE range from normal to severe elevations. Also, ANE has elevated CSF proteins which is not seen in Reye's syndrome. Diffuse cerebral edema is the neuro radiological hallmark of Reye's, followed by involvement of bilateral thalami and brainstem; while symmetric thalamic necrosis and haemorrhage is the most common finding in ANE.\(^\text{14}\) ADEM is differentiated from ANE by the asymmetry of the radiological findings, absence of necrosis and haemorrhage as well as perivascular distribution.\(^\text{1,14}\) It was also observed that bilateral thalamic involvement was the most consistent finding (100%), followed by involvement of the sub-cortical white matter. The same has been supported by the previous literature.\(^\text{12}\)

Elevation in CSF proteins was seen in three (17.6%) patients. CSF protein has been shown to be valuable in prognostication as it reflects increased permeability of the blood-brain barrier and destruction of brain parenchyma. However, as only 2 patients had elevated proteins, it limits our ability to correlate it with increased mortality.\(^\text{20}\)

So far, there are no treatment guidelines for the treatment of ANE. As Wu et al. stated that mainstay of the treatment is intensive care, symptomatic and empirical treatment including anti-epileptic drugs, antibiotics and antivirals along with the immuno-modulatory agents.\(^\text{20}\) The management of our patients was symptomatic and supportive; antibiotics and antivirals were administered to all patients and anticonvulsants were started at the initial presentation.

The clinical course is fulminant and diverse, the spectrum ranging from complete recovery to severe sequelae and death.\(^\text{21}\) This study showed 23% of the children had no complications, 50.2% of the children developed severe neurodevelopmental complications and 17.6% died during hospital stay.

Yamamoto et al. demonstrated that the outcome was not affected by the treatment modality, rather the poor outcome correlated with the presence of brain lesions, shock on presentation as well as age >48 months.\(^\text{15}\) Similarly, in this study, the outcome was affected by the clinical severity as (3/11) of the patients requiring PICU admission died; while 72% (8/11) developed severe neurological sequelae. Hoshino et al. from Japan showed the incidence of full recovery, mild to moderate sequelae, severe sequelae, and death being 12.8%, 23%, 33.3%, and 28.2%, respectively.\(^\text{22}\) Another study by Lim et al. showed mortality of 14%,\(^\text{23}\) Even though, the spectrum of neurological complications associated with ANE is broad, children usually developed chronic disabilities as in our group of patients.\(^\text{23}\)

This is the first comprehensive report from a developing country with the largest patient cohort. The limitations in our study can be attributed to representing a single centre with a small sample size, limited resources in conducting extensive virological studies, metabolic workup and repeated imaging studies to monitor the changes in brain along the course of the disease. Further research is needed for early identification and intervention to enable us to improve survival as well as the quality of life of these individuals.

**CONCLUSION**

ANE is a rapidly progressive neurological disease with grave outcome. The exact pathogenesis is yet to be
elucidated. Use of antivirals and immunomodulation does not alter the course of disease and the outcome depends upon the severity at the time of initial presentation.

REFERENCES


