

AES: Clinical Presentation and Dilemmas in Critical Care Management

Mahima Mittal*, K. P. Kushwaha**

Abstract

Acute encephalitis syndrome (AES) is an epidemiological term used for surveillance of encephalitis. Worldwide, reported incidences of encephalitis range from 6.3 to 7.4 per 100,000 for all ages (adults and children) and approximately 10.5-13.8 per 100,000 children. The most common cause of AES is viral but definitive diagnosis remains elusive in most cases.

Gorakhpur and adjoining areas have been witnessing seasonal outbreaks since 1978. Over the past few years, the clinical pattern of the epidemics has changed with patients having multisystem involvement rather than isolated neurological involvement. The percentage of Japanese encephalitis positive cases have also declined and few studies have identified Enteroviruses as a possible cause, but the exact aetiology still remains undetermined. The changing clinical presentations have also posed a challenge towards the optimal management of patients of encephalitis. The management of AES does not end with acute illness, but prolonged neurological deficits are common, needing not only medical but educational and vocational support, and physiotherapy as well. Evidence based guidelines for diagnosis and treatment of these cases is required.

Keywords: AES, Japanese Encephalitis, Clinical Presentations.

Introduction

Encephalitis is defined as an inflammation of the brain with clinical evidence of neurologic dysfunction. It is mostly caused due to a viral infection, sometimes due to other infective organisms and rarely due to non-infective pathology like acute disseminated encephalomyelitis (ADEM). However, despite extensive testing, the aetiology of encephalitis remains unknown in most patients.¹

Japanese Encephalitis virus is a leading cause of viral encephalitis in Asia, where about 50,000 cases and 10,000 deaths are reported each year, mostly among children. Officially reported cases of JE greatly under-represent the true prevalence, due to incomplete surveillance in many affected areas. The high case fatality rate (20%–30%) and frequent residual neuropsychiatric damage in survivors (50%–70%) made JE a major public

health problem. To identify high risk areas for appropriate public health response and document the impact of control measures, the term 'Acute Encephalitic Syndrome'² was devised by WHO in 2006. This term is now being used for surveillance in all encephalitis endemic zones irrespective of the aetiology. Clinically, a case of Acute encephalitis syndrome (AES) is defined as a person of any age, at any time of year with the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) AND/OR new onset of seizures (excluding simple febrile seizures). Other early clinical findings in AES may include an increase in irritability, somnolence, or abnormal behaviour greater than that seen with usual febrile illness.²

First epidemic of Japanese encephalitis occurred

* Associate Professor, Department of Paediatrics, B.R.D. Medical College, Gorakhpur

** Professor & Head, Department of Paediatrics, B.R.D. Medical College, Gorakhpur

Correspondence to: Dr.K.P.Kushwaha, Professor & Head, Department of Paediatrics, B.R.D. Medical College, Gorakhpur, U.P. India. **E-mail:** komal.kushwaha@gmail.com

in 1978 and after that, seasonal outbreaks of Japanese Encephalitis occurred with striking regularity in Gorakhpur and adjoining areas that lead to substantial mortality. JE continued to be the main cause of encephalitis till 2005. A change in the AES landscape in this region was noticed after 2005.³ Although Japanese encephalitis virus (JEV) is still the key etiological agent for AES in this region, many recent studies suggest that Enteroviruses^{4,5} may account for outbreaks of AES here. A definite change in the clinico-epidemiological profile has been noted in the patients after 2005 epidemic. Nehru Hospital of Baba Raghav Das Medical College is the most approachable tertiary care hospital for a population of 50 million of eastern UP, parts of Bihar and adjoining Nepal, and has witnessed all epidemics right from 1978.⁶ The annual admission rate for AES is approximately 2000- 2500 patients/year. This review of encephalitis is mainly based on the cases seen in this institution.

Scenario worldwide

In western settings, reported incidences of encephalitis range from 6.3 to 7.4 per 100,000 for all ages (adults and children) and approximately 10.5-13.8 per 100,000 children.⁷ An estimated 700 cases of viral encephalitis occur yearly in England, of which about 7% are fatal, which is highly underestimated⁸. In USA, the yearly national cost of hospital care of patients taken to hospital with encephalitis associated illness has been estimated at US\$630 million.⁹ In Asia, more than 133,000 children suffer from Acute Encephalitis Syndrome (AES) annually.⁷

There are a large number of causative agents (bacterial, parasitic, fungal, and viral) that can cause a syndrome of AES. Defining the causal relationship between a microbe and encephalitis is complex. Over 100 different infectious agents may cause encephalitis, often as one of the rarer manifestations of infection. Granerod et al.^{10,11} (2010) gives a detailed account of etiological entities. Herpesviruses and Enteroviruses were the leading definitive causes identified in the US.^{12,13} Studies from England show herpes simplex virus, ADEM, antibody associated causes¹⁴ (NMDA receptor antibodies and voltage-gated potassium channel antibodies), varicella zoster virus, and M tuberculosis as the commonest aetiologies.¹⁵ First isolated in California, USA, in 1969, Enterovirus 71 (EV71) is a major public health issue across the Asia-Pacific region. In a

study by Glaser et al.,¹⁶ involving a total of 170 patients, the most commonly identified viral agents were EV (25%) and HSV-1 (24%).

Indian scenario

Epidemics in India were first reported in mid 1950s, JE virus was first detected in India in 1955.¹⁷ A recent review about changing trends in India, including most studies from 1975 to 1999, identified JEV as the main cause of AES, and many studies published after 2000 identified Enteroviruses and Chandipura as the most common agents, in both outbreaks and surveillance studies.¹⁸

Large outbreaks of chikungunya¹⁹ and dengue²⁰, Nipah²¹ and Chandipura^{22,23} have been reported to cause large scale outbreaks in various parts of the country. West Nile virus encephalitis^{24,25} that has been detected as sporadic illness earlier, also seems to be emerging as an outbreak in Assam and Kerala. Herpes simplex virus encephalitis (HSE) is the most common cause of sporadic fatal viral encephalitis in the West,²⁶ but in India it occurs as a sporadic illness.

Emerging Viral Agents and Changing Epidemiology

The changing epidemiology and newer viral agents causing AES in India have recently been reviewed.^{18,27,28} Various other viral agents e.g., Human Parvovirus 4,²⁹ West Nile virus,^{24,25} Bagaza virus,³⁰ Coxsackie virus³¹ have been reported in sporadic AES cases from India. Studies from southern India have reported encephalitis due to EV 26.³² In a study in the year 2004- 2006 EV71 was reported from western Uttar Pradesh also.³³ Spirochetal zoonosis like leptospirosis is also an emerging infection in some parts of India,^{34,35} causing manifestations of AES. Various non-viral causes associated with encephalitis were also described.³⁶ Some authors have also reported epidemic-like occurrence of AES due to non-infective causes in children from India e.g., plant toxins (*Cassia occidentalis*),³⁶ heat stroke^{37,38} and Reye's syndrome^{39,40}. The exact epidemiologic significance of some of these reports is difficult to elucidate from the available literature.

Gorakhpur scenario

The Eastern districts of Uttar Pradesh, which share a border with Nepal and Bihar, have been experiencing periodic outbreaks (every 1- 3

years) of JEV since 1978 (table- 1). Encephalitis is reported mainly from eight districts of Eastern UP with the highest number of cases occurring in Gorakhpur, Kushinagar, Maharajganj, & Deoria and two adjoining districts of Bihar (Gopalganj and West Champaran). There were three epidemics back to back in Uttar Pradesh in 1978, 1980 and 1988^{41, 42} preceded by heavy rainfall. The incidence of Japanese Encephalitis (JE) showed an increasing trend from 1982 to 1988. Total number of annual cases and case fatality rate (CFR) rose from 118 and 23.7 per cent in 1982 to 772 and 32.2 per cent in 1988 respectively. A definite increase was noticed in the number of cases per block in 1984 and 1987.

Between July and December 2005, a large and severe epidemic of viral encephalitis was seen. During this period, a total of 6097 JE cases with 1,398 deaths were reported.^{43, 44} Samples from patients during 2005 epidemic confirmed the presence of JE genotype 3.⁴⁵ The comparison of historical percentages of JE with the present scenario may not be completely accurate as different diagnostic tests with differing sensitivity and specificity have been used earlier. Diagnosis of JE till 1989 was done using HAI test in unpaired sera, and with paired sera after that. Mac ELISA, considered to be a more specific diagnostic test has been used since 2002.

Year	No. of Cases	Mortality	Mortality in %
1978	274	58	21
1979	109	26	24
1980	280	66	24
1981	56	22	39
1982	86	23	27
1983	126	32	25
1984	68	26	48
1985	234	105	45
1986	176	81	46
1987	74	23	31
1988	875	278	32
1989	13	2	15
1990	313	103	33
1991	441	160	36
1992	305	109	36
1993	127	53	42
1994	300	107	36
1995	490	152	31
1996	519	181	35
1997	160	53	33

1998	804	161	20
1999	787	205	26
2000	646	151	21
2001	787	168	24
2002	540	127	20
2003	952	191	25
2004	876	215	28
2005	3532	937	26.52
2006	1940	431	22.21
2007	2423	516	21.29
2008	2194	458	20.87
2009	2663	525	19.71
2010	3303	514	15.56
2011	3308	627	18.95
2012	2517	527	20.86
2013	2110	619	29.33

Table 1. Year Wise Admissions & Mortality in BRD Medical College, Gorakhpur

In 2006,^{46, 47} large scale campaign vaccination was done in Gorakhpur and Basti districts and 68,36,506 children between 1- 15 yrs of age (information from DGME office, U.P.2014, UNICEF coverage report document, 2008) were vaccinated during the months of May- June. This large scale vaccination against JE in 2006 resulted in an increase in protective antibodies against JE. A serosurvey done by NIV in collaboration with PATH, after the vaccination drive, found that the seropositivity in the population had increased from 68% to 88% (M.M. Gore personal communication).

In the year 2006, a marked change in clinical trend of patients presenting with AES was noted. Investigations also showed a decreased JE positivity (10-15%). National Institute of Virology showed positivity to Enterovirus (EV) in 66 (21.6%) of 306 patients by RTPCR. Sequencing and phylogenetic analyses of PCR products from 59 (89.3%) of 66 specimens showed similarity with EV-89 and EV-76 sequences.⁴ In the following years CSF samples showed the presence of some Enterovirus in the

2- 3% cases. In addition, Enteroviruses have consistently been isolated from the rectal swabs in 30- 40% cases since 2008 (unpublished data). At present, JE positivity ranges between 7- 15%.

According to a similar study published from a tertiary care teaching hospital of Lucknow,³¹ out of 204 children with encephalitis over a period of 2 years (2009 to 2010), Enterovirus was detected in 45 specimens (22.1%). Molecular typing of Enterovirus revealed the predominance of echovirus 21, echovirus 1, coxsackievirus B1, enterovirus 75, enterovirus 76, coxsackievirus B5, and echovirus 19.

Hence there has been a change in the landscape of AES in Gorakhpur in the previous few years, and both outbreak investigations and surveillance studies have increasingly reported non- JE aetiologies.

Epidemiology in Gorakhpur

The geographic features of this region are conducive for the spread of JEV; an abundance

of rice fields and a bowl-shaped landscape allow water to collect in pools. Heavy rains saturated the ground in 2005, which caused ideal breeding conditions for mosquitoes that transmit the virus from pigs to humans. In addition, high temperature and relative humidity provided a suitable environment for JEV transmission. Poor sanitary conditions, water logging, improper sewage disposal, etc have led to a surge of other waterborne illnesses too in this region. Clustering of cases of AES during the rainy season and etiological studies point towards the possibility of a water borne viral illness being the culprit.^{3,45}

For epidemics in Gorakhpur, seasonal trend from 1978- 2005 was spread from July to October.⁴¹ From 2006 onwards, the AES cases were seen throughout the year, although the seasonal peak as seen in JE epidemics persisted. This has also been demonstrated by Kumar et al.³¹ from Lucknow. On comparing the patients who were JE positive and those who were not, a difference in age was also noticed. For JE patients, a median age is four years [interquartile range (IQR), 8–13] and for non- JE patients, it is 4.5 years (IQR, 6–13). Ten years back, the common age was 6- 12 years.³¹ Male to female ratio has been the same throughout and is in favour of males. Patients mostly belong to a low socioeconomic status, 60% go for open field defecation and about 55% use shallow handpumps for drinking water. CFR in JE epidemics was reported to range between 23-32%⁴⁸ while CFR in later epidemics ranged from 19- 25%.³

Pathogenesis and Pathology

Encephalitis is caused by direct invasion and destruction of neural tissue by actively multiplying viruses or by a host reaction to antigen. Certain viruses are believed to cause neuronal injury through a proinflammatory cytokine and chemokine cascade that occurs upon activation of astrocytes and microglia. It has been demonstrated that various pro-inflammatory molecules including IL-1 β , MCP-1 (CCL-2), IFN- α , TNF- α , RANTES (CCL-5), IL-6, and IL-8 are elevated in JE patients.⁴⁹ These molecules are also considered as early biomarkers for disease identification.⁵⁰ A similar rise in cytokine levels was demonstrated in AES (both JE positive and JE negative) cases in this area.⁵¹ Recent studies in China have also demonstrated the role of cytokines in the pathogenesis of enteroviral infections.⁵² Different viral infections are known to involve

different organs of the body either due to direct viraemia or due to the proinflammatory cytokine and chemokine cascade.⁵³

Consent for autopsy is difficult to obtain, but tissue biopsies were obtained postmortem from various sites. Tissue sections of the brain generally were characterized by meningeal congestion and mononuclear infiltration, perivascular cuffs of lymphocytes and plasma cells, some perivascular tissue necrosis with myelin breakdown, and neuronal disruption in various stages, including, ultimately, neuronophagia and endothelial proliferation and necrosis.

Cardiac biopsies revealed evidence of active myocarditis in the form of focal or diffuse, mixed inflammation, degenerating and necrotic myofibres, and occasional giant cell. In the liver, the histopathological findings were focal fatty change, mild inflammation, Kupffer cell hyperplasia, and intracellular bile stagnation. The features of acute tubular necrosis were observed in the kidney tissues along with mild inflammation and features of interstitial nephritis in three cases. In addition, cellular and hyaline tubular casts were observed in one case. The examination of muscle revealed focal mild inflammation without myofibre necrosis (unpublished data).

Clinical Manifestations

Over the years, epidemics in Gorakhpur have seen a change in the clinical trend and the spectrum of illness in this region. Clinical features described during JE epidemics (1978-2005) mainly consisted of fever (100%), convulsions (73- 82%), altered sensorium (78-100%), headache (68- 71%), hypertonia (50-77%), signs of meningeal irritation (25-35%), extrapyramidal features like rigidity, posturing and movement disorder in (15- 30%) cases.^{40, 42, 54} Focal deficits (45%) and cranial nerve palsies were also reported⁵⁴ (6.5%). These features are usually seen in confirmed cases of JE⁵⁵ (table 2).

S. No.	Clinical Features	Percentage
1	Fever	100
2	Headache	68-71
3	Vomiting	60
4	Diarrhoea	55
5	Convulsions	73-82
6	Altered Sensorium	78-100
7	Cranial Nerve Palsies	6.5
8	Signs of meningeal irritation	25-35
9	Peripheral Vascular Failure	4.5
10	Involuntary movements/ Dystonia	15-30
11	Focal deficits	30-45
12	Hypertonia	50-77

Table 2. Clinical Features of Japanese Encephalitis

After campaign vaccination of JE in 2006, the clinical presentation of AES cases changed.³ These patients had CNS features of encephalitis, but along with that the signs of cardiovascular, respiratory system, renal involvement were noted (table 3). Apart from this, there was a presence of rash in a fair number of cases.

S. No.	Clinical Features	Percentage
1	Fever	80-100
2	Altered sensorium	70-80
3	Convulsion	75-80
4	Swelling of body	60-70
5	Pallor	15-20
6	Vomiting	60
7	Diarrhoea	55
8	Breathlessness	27-30
9	Hand foot and mouth lesions	3-5
10	Rashes over the body	15-20
11	Abdominal pain	40
12	Floppiness	20-30
13	Splenomegaly	20-25
14	Hepatomegaly	80-85
15	CHF	40-45

Table 3. Clinical Features of Non- JE Cases

A non specific viral rash sometimes resembling HFMD⁵⁶ is seen in about 3% cases. Many (15-20%) children with AES present with an atypical maculopapular rash (dark dirty rash) with distribution on face and extremities. Rashes may be seen in other encephalitides; for example, a maculopapular or vesicular rash is seen in Rickettsial infections or the highly typical rash of measles virus infection.¹ Childhood exanthema can also be seen in many Enteroviruses that can cause HFMD or herpangina, EV71 and coxsackievirus type A 16 being the most frequent, and both can cause epidemic disease. Coxsackievirus type A 16 is not generally associated with neurological disease,⁵⁷ but the rash it causes is indistinguishable from that caused by EV71. Two particularly important causes to be considered are meningococcus, because of the need for antimicrobial treatments, and dengue, because of the risk of developing dengue haemorrhagic fever, as severe forms require careful fluid resuscitation.^{56, 58}

Cardiovascular manifestations (40%) like gallop rhythm, muffled heart sounds, tachycardia, tachypnea, hepatomegaly and basal crepts/rhonchi along with abnormal liver enzymes and ECG abnormalities like ST depression, sinus tachycardia, low voltages, prolonged PR interval, conduction defects suggested presence of myocarditis.^{3, 59, 60} Pulmonary oedema was also present in around 13- 18% of these cases^{3, 59} which is also described in EV71 infection.⁵³ Elevation of cardiac enzymes i.e. CPK-MB, ALT, Troponin I suggestive of myocarditis^{59, 61} is also seen in 30- 40% patients. Chest radiographs show cardiomegaly, and with mean cardiothoracic ratio of 90% subjects in a study⁶¹ being 62 ± 5.8 (SD) cases and features of pulmonary congestion in 18% cases. Echocardiographic findings showed regional wall hypokinesia, pericardial effusion, dilatation of left ventricle, decreased ejection fraction and increased mean end diastolic diameter, all in favour of myocarditis.⁶² Cardiac MRI, a newer non invasive technique with high sensitivity and specificity^{62, 63} was performed in patients and regional wall enhancement and pericarditis were reported in few.

Nonoliguric renal derangement is present in approximately 15% patients and usually mild azotemia with mildly deranged levels of serum creatinine are seen. Acute kidney injury due to Enterovirus 71 and influenza virus has been documented in some case reports.⁶⁴

Common presenting complaints in patients were mainly headache (90%), abdominal pain (40%), vomiting (60%), and diarrhoea (55%). Facial puffiness and pedal oedema were present in 70% cases. An abnormal cytokine activation that produces a severe inflammatory response, leading to leaky capillaries could be one of the possible reason^{52, 59} of oedema. Another reason could be cardiac failure due to myocarditis.

Central nervous system involvement in these patients was characterized by convulsions and floppiness, signs of meningeal irritation and altered sensorium. Encephalitis associated with gastrointestinal symptoms includes infection with enteroviruses, rotavirus, and human parechoviruses.⁶⁵⁻⁶⁹ 19- 20% of children come with status epilepticus and they have poorer prognosis. In survivors of encephalitis, EEG recordings remained abnormal in 18% children up to 6 months follow-up. In the Toronto Acute Childhood Encephalitis study,⁷¹ 50 children with suspected encephalitis were reported with the most common presenting features being fever (80%), seizures (78%), focal neurological signs (78%) and decreased consciousness (47%). In Wang's study⁷² from Taiwan, 101 children with a final diagnosis of encephalitis were reported to have the following features: change in personality or reduction in consciousness (40%), seizures (33%), new neurological signs (36%), and meningism (22%). Encephalitis with an acute flaccid paralysis is a characteristic of polio, and other enteroviruses, such as enterovirus 71, as well as flaviviruses.⁵⁶ A study of 144 (134 children) patients with encephalitis due to Japanese encephalitis virus, showed that 40 patients had witnessed seizures in hospital. Of these, 25 had one or more episodes of status epilepticus including 15 who went on to develop subtle motor status. Patients with witnessed convulsive or subtle motor status epilepticus were more likely to die ($p < 0.0003$).⁷³ EEG is thus a recommendation in all such cases.¹

In an unpublished study done in the department of paediatrics BRD medical college, Gorakhpur, in 2004, CT scan was abnormal in 80% patients. Common injuries were thalamic (40%), basal ganglia (24%), and cortical (40%). Similar CT scan changes have been described in other studies in JE positive cases as well.^{54, 74} Newer studies, in the department, on AES reveal subtle atrophic changes (50%) and cerebral oedema (10%) on CT scan. Meningeal enhancement (2%), and hypodensities (6%) were also noticed in a few cases.

Respiratory symptoms especially tachypnea is consistently present. This respiratory distress although is mostly due to cardiac involvement, but persistence of cough and respiratory symptoms even months after resolution of congestive cardiac failure and presence of radiography findings suggestive of chronic lung disease, point to direct lung injury also. Enterovirus71 has been known to cause significant respiratory involvement. Hepatomegaly is a consistent feature in about 80% cases and splenomegaly is found in 20% cases.

Studies performed for clinical delineation of these cases have revealed a difference between the two groups viz, JE positive, and JE negative cases also termed as non JE. High grade fever, headache, vomiting, hypertonia, abnormal movement, focal neurological deficits and extra-pyramidal signs were present in JE positive patients.³ But spectrum of illness in JE negative cases (non JE) was entirely different,^{3, 60} moderate- grade fever, swelling over body (70%), floppiness and hypotonia (15- 20%), rash (20%) (mostly maculopapular), splenomegaly (20%) and hepatomegaly (40%) were present in JE negative patients. Hypotonia, hepatomegaly, splenomegaly, hepatosplenomegaly and cardiovascular system involvement were dominant features in the non- JE group. Multivariate analysis by logistic regression revealed three clinical signs – peripheral vascular failure, splenomegaly and hypotonia– to be independent distinguishing clinical signs in non-JE patients.^{3, 60}

Combination of symptomatology suggests an infection with a multi- organ involvement and the most important of them are CNS involvement and cardiopulmonary involvement. A similar disease complex is reported in certain enteroviral infections.⁵⁶

Lab investigations

Patients of AES demonstrate clear CSF, mild mononuclear pleocytosis (usually less than 150 cells /cmm) and level of CSF proteins ranges from 40 to 100 mgs percent and sugar is normal. Haemoglobin levels suggest mild to moderate anaemia 8.5- 10 mg/dl and thrombocytopenia (<50,000 cell/mm³) is seen in around 20% cases. Mild to moderate anaemia could be dilutional or due to the nutritional status. Anaemia in these cases however was usually normocytic normochromic type. Some viruses like

parvovirus and Dengue are known to cause thrombocytopenia.

Serum transaminase (AST and ALT) levels are raised in almost all cases and average ALT level ranges from 48-111U/dl and average AST level ranges from 45- 150U/dl. A modest rise in ALT levels could be attributed to passive congestion due to heart failure. But presence of inflammatory cells in liver biopsy could suggest direct damage also. In few studies, AST levels are considered good markers for myocarditis suspicion.⁶¹ Average creatinine level ranges from 0.7- 0.9 mg/dl and when age specific creatinine levels were analysed, it was found that about 60% had mildly raised creatinine. Mild azotemia (45- 51mg/dl) is found in approximately 10- 25% cases.

Serum sodium is usually low⁷⁵ (<135meq/dl) in about 35- 40% cases. Serum potassium levels are deranged in about 25% cases and usually mild hypokalemia is found and could be attributed to the fact that most children of AES are undernourished.⁷⁶

Management

Internationally ,various guidelines on evaluation and management of suspected Acute encephalitic syndrome have been proposed by a number of groups- Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group National Guidelines (2008),¹ Clinical Practice Guidelines by the Infectious Diseases Society (2008),⁷⁷ EFNS guidelines,⁷⁸ 2009 the International Encephalitis Consortium guidelines, 2012⁸⁰ and many more.

Guidelines had previously been provided by ICMR in 1978; in India, for JE management at the community level by PATH: Japanese Encephalitis Clinical Care Guidelines, 2005,⁸⁰ UNICEF and Government of India (Facility-based IMNCI Participants' Manual⁸¹ and an India Expert Group on Viral Encephalitis Consensus Guidelines on Evaluation and Management of Suspected Acute Viral Encephalitis in Children in India, 2012.⁸²

Mostly all guidelines stress on the identification and treatment of neurological features viz. raised intracranial tension, seizures and cerebral oedema, and systemic features viz. fever, hypoxemia, hypotension, low cerebral perfusion pressure, and metabolic disturbances, with minor differences depending on the aetiology and clinical presentation.

Seizure is one of the most common presentations requiring anticonvulsant therapy. Delay in treatment in such cases leads to further damage and 20- 30% land up into status epilepticus, approximately 20% of such cases need more than one anticonvulsant for seizure control and have a poorer prognosis. Approximately 10- 25% cases have impending respiratory failure and require ventilator support. As most patients who come to our hospital are from far-off places and have been unconscious for long, possibility of hypovolemia and hypoglycaemia is strong and hence all of them are given intravenous fluids and a bolus of 10% dextrose at admission.

Management of cerebral oedema in our patients is similar to any other protocol except for mannitol, which is used sparingly in our set up because mannitol⁸³ causes plasma volume expansion and is excreted unchanged in urine and since most of our patients have a compromised heart and decreased renal function, chances of it causing volume overload is high. In routine paediatric practice, the most common cause of shock and peripheral vascular failure is hypovolaemia and dehydration, for example after gastrointestinal infection. These disorders are treated with rapid fluid resuscitation but when approaches were used in the early EV- 71 outbreaks in Asia, they frequently precipitated pulmonary oedema.⁵⁶ After this, it became clear that impaired cardiac function is an important contributor to shock. Clinicians were more judicious in their use of intravenous fluids and used ionotrope support. In patients with features of cardiac involvement, fluids and ionotropes like dopamine and dobutamine are added early, saline for peripheral vascular failure and 5% dextrose in normal saline as maintenance dose is used.

Electrolyte imbalances are treated accordingly. Hyponatremia requires special mention as it is commonly found (35- 40%), and thus hypotonic solutions might aggravate the problem and cause further damage. Recognition of the type (isovolumic, hypovolumic, hypervolumic) is important. Treatment is done as per clinical practice guidelines by Nephrology Dialysis Transplantation.⁸⁴ Fluids resuscitation is restricted (2/3rd of requirement), sodium deficit is calculated and in severe hyponatremia (<130meq/dl) rapid correction with 3% saline is advocated. Deficit is calculated using Adrogue-Madias formula⁸² (change in serum Na⁺ = 1/4 infusate Na⁺ - serum Na⁺/total body water + 1)

The role of corticosteroids in the treatment of viral encephalitis is not established. However, corticosteroids may be considered along with acyclovir in patients with marked cerebral oedema, brain shift or raised intracranial pressure. Their role remains controversial because steroids may theoretically increase viral replication.¹ However, steroids are recommended in ADEM and autoimmune encephalitis.⁸²

British and American guidelines¹ stress on the use of acyclovir within 6 hours of admission as HSV is one of the commonest cause of encephalitis in industrialized countries and the only organism that has an available specific treatment. Indian scenario is however different. Cases of herpes encephalitis are found to occur sporadically but are not known to cause epidemics. Positivity for HSV is only 2- 3% in our setup. So use is limited only to cases with CSF PCR positivity for HSV. Trials on drugs like oral ribavirin were not found to be useful in children with Japanese B encephalitis in a randomized controlled trial.⁸⁶ There is experimental evidence of benefit of minocycline in JE.⁸⁷ A study conducted here, showed a reduction in hospital stay and better recovery on 6 months follow- up, in JE positive patients who were given minocycline.⁸⁸ Rickettsial infections are increasingly being reported in various parts of India⁸⁹ and early treatment is recommended to save lives.^{90, 91} Empirical use of doxycycline in doses of 10mg/kg for 5 days, in an unpublished data in our setup, in patients with high suspicion of rickettsial infection⁸⁹ has not shown any difference in mortality or duration of hospital stay.

Myocarditis and congestive cardiac failure are common concurrent features in AES patients and require special mention. Management of CHF is based on European Society of Cardiology 2008 guidelines.⁹² Use of loop diuretics like frusemide has shown to benefit patients of AES having features of congestive cardiac failure. Patients who are hypotensive may require ionotropes and milrinone.^{94, 96} The results of a small, non-randomised, retrospective assessment of 24 children with EV71- induced pulmonary oedema showed that those treated with milrinone had reduced tachycardia and lower mortality than those who did not receive this drug.^{93, 94} Carnitine (100 mg/kg/day) is also being used in patients with myocarditis. Low dose digoxin or ACE inhibitors with the persistence of symptoms after the acute phase is over are also recommended.⁹⁵

IVIG in viral myocarditis is the most commonly studied therapeutic intervention to prevent the autoimmune myocardial damage.^{57, 96, 98, 99, 100} Non randomized⁵⁹ and randomized¹⁰¹ studies conducted in our institution have shown to be useful in reducing mortality and improvement in ejection fraction in myocarditis. A total of 83 consecutive children of acute encephalitis syndrome complicated by myocarditis were allocated to the two groups based on the days of the week - those presenting on Monday and Friday were allocated to IVIG treatment (group I) and those presenting on the other days to standard care (group II). Group I (n= 26) patients received intravenous immunoglobulin at a dose of 400mg/kg/day for 5 days in addition to standard care. Mortality was lower in the IVIG group (n=1, 3.8%) patients as compared to the standard care group (n=13, 22.8%) patients with relative risk of 0.17 (95%, CI: 0.02, 1.22). The difference in mortality reached borderline significance with the p value being 0.05. At discharge, the mean (SD) ejection fraction improved from 32.8% (6.31) to 49.5% (9.04) in group I patients which was significantly higher than the group II patients (p=0.001). Larger placebo controlled randomized phase two trials are still needed.

Prognosis

Encephalitis is a severe disease of the brain with about 20- 30% mortality. Several prognostic factors for death or severe outcome in encephalitis have been proposed.¹⁰⁰ Risk factors for mortality among non- JE patient's in various studies in BRD Medical College were gastrointestinal bleed, requirement of ventilator support within 48 hours of admission, peripheral vascular failure and pallor.^{3, 76} Various long term and short term studies have recorded residual deficits in survivors. Internationally, JE and enterovirus encephalitis have been studied in detail, while in India, studies are mainly restricted to JE. The proportion of patients reported to have severe sequelae after infection varies widely, from 19 to 71%.

The long- term effects of CNS enterovirus infections were examined in 19 children after 17 to 67 months. Three children (16%) had definite neurologic impairment, five (26%) had possible impairment, and 11 (58%) were free of detectable abnormalities. Enterovirus 71 infections with CNS involvement and cardiopulmonary failure may be associated with neurologic sequelae, delayed neurodevelopment,

and reduced cognitive functioning. Children with CNS involvement with cardiopulmonary failure did not do well on neurodevelopment tests.¹⁰² Limb weakness and atrophy were also detected in many children in this study. Head circumference growth, depressed language, and speech skills were more affected in children who were affected during the first year of life than children who were affected after the first year of life.¹⁰³ In another study, 80% children had no deficit while 14.3% had residual deficits in terms of severe motor and respiratory failures after about two years.¹⁰⁴

In a Chinese study with 85 JE patients assessing residual effects after 6- 27 years, 22% of JE patients had objective neurologic deficits and 28% had subnormal IQs. Abnormal activities of daily living (ADL) scores were only noted in 15% JE patients.¹⁰⁵ Solomon and his group have developed a scale and its results have been found to be consistent even when done by different interviewers across various locations. The questionnaire takes about 15 min to fill up and can be used as tool for conducting large surveys.¹⁰⁶ Ooi et al. (2008)⁵⁶ studied a set of 108 patients and observed that at the time of discharge from the hospital 44 (41%) of the 108 patients who survived had apparent full recovery; 3(3%) had mild, 28 (26%) had moderate, and 33 (31%) had severe neurological sequelae. A further follow up of 86 children for about 4 years revealed that 31 (36%) recorded improvement while 15 (17%) showed further deterioration. Assessment after 3- 6 months was a better predictor of long term sequelae rather than at the time of discharge.

Indian studies have been mainly restricted to studies carried out on JE in UP. The reported frequency of acute symptomatic seizures in JE is 7- 46%.¹⁰⁷ Children with JE are more likely to have dystonia and a poor outcome at six months compared to adults.¹⁰⁸ Parkinson symptoms were also detected. In patients with Parkinson signs along with dystonia, the residual deficit persisted in a higher number of individuals.¹⁰⁹ In a study of 55 children followed up after 12- 18 months and 22 of these even after 2 years, a high rate of major sequelae (45.5%) in the form of frank motor deficits (32.7%), mental retardation (21.8%) and/ or convulsions (18.2%) was observed. Neurological deficits were of diverse types and improved even after 2 yr of the illness. 14 patients (25.4%) had only minor deficits in the form of scholastic backwardness, behavioural problems, and/ or subtle neurological signs. Only

16 (29.2%) patients were completely normal on follow up.¹¹⁰ In a study in Assam, residual symptoms remained in about one third of cases even after one year.¹¹¹

Paediatrics Department at BRD Medical College also has followed and recorded long term residual illness in children with JE during 1981 outbreak. Out of 429 cases contacted, 58 responded. Only 36 (57.1%) were reported to be normal. Out of the remaining 22 cases, most of them had higher function impairments, while seven had neurological deficit and convulsive disorders. More importantly, psychological disorders were seen in 15/22 cases.

Dystonia and the related spastic changes that are seen in severe JE cases cause a great degree of disability. A few centres carry out corrective surgeries to correct the postural changes. Use of prosthetics might also be needed in few cases. In case of milder muscular problems, a corrective physiotherapy can help children. Relief from abnormal daily living activities also cause a lot of problems for the family members, and a consistent long term training procedures are needed for correcting these. Parents and attendants of JE patients would need a lot of education and training in solving this problem.

Follow up studies on non- JE AES cases have shown various disabilities. Physical disabilities in the form of paresis are seen in 75% of the cases, while dystonia is seen in about 10% of the cases. This improves to about 10% and 6% in two years follow up. Mental retardation, seizures, involuntary movements are seen in 80-98% of the children at the time of discharge, which reduces to 23%- 10% after two years. Psychological and behavioural changes that are seen in about 5 to 56% cases improved in two years. However, incontinence, abnormal behaviour and irritability remains in 5%, 18%, and 18% of the children respectively even after two years. Follow up of the children having AES with myocarditis has not been done systematically. However, long term cardio pulmonary problems are known to be associated with myocarditis.

Conclusions

Epidemics of AES in Eastern UP continue to pose a considerable challenge to the medical fraternity in identifying the aetiology and establishing the diagnosis. However, two distinct clinical trends are clearly evident, one, which supports the diagnosis of Japanese encephalitis,

and where treatment is mainly aimed at the management of CNS symptoms and advanced life support; the other one pertains to those patients who have a multi organ involvement at presentation. Apart from neurological features, the most predominant involvement is that of the cardiovascular system which is particularly challenging to treat. Rash, hepatosplenomegaly, floppiness, mild azotemia, increased serum transaminases are some of the features which set these patients apart. As the aetiology is unidentified, the management is largely symptomatic. Uses of acyclovir as per the British guidelines, milrinone in CHF, and IVIG in fulminant myocarditis are some of the dilemmas, which need more research for clarification.

Mortality is high and the magnitude of the problem is compounded by the fact that the survivors are left with long term sequelae, not only pertaining to the central nervous system, but other organs as well. There are numerous lacunae in our knowledge, and evidence based clinical practice guidelines for diagnosis and treatment of these patients would considerably help in the management of these epidemics.

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