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Study of acute encephalitis syndrome in children

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Abstract

Objective: *To determine the profile and outcome of children admitted with Acute Encephalitis Syndrome (AES) and to find out the prevalence of Japanese Encephalitis (JE) IgM antibodies positive cases among these patients with their case fatality rate (CFR).*

Materials and methods: *Study consist of retrospective analysis of hospital records of children up to 15 years of age admitted with diagnosis of AES in pediatric wards of College of Medical Sciences- Teaching Hospital, Bharatpur from January 2007 to December 2008.*

Results: *During two years, 61 patients of AES were admitted. Male and female patients were 33 and 28 respectively. Meningitis accounted for 29 and encephalitis for 32 patients. JE IgM seropositive cases contributed for 18% of all AES cases. Case fatality for JE was 16.6%.*

Conclusions: *Japanese Encephalitis is endemic in catchment area of the hospital. JE has significant morbidity and mortality which can be prevented by immunization and mortality can be reduced if supportive interventions are provided in time.*

Key words*: AES, JE, CFR.*

Introduction

Encephalitis refers to acute inflammatory process affecting the brain. AES may present as encephalitis, meningoencephalitis or meningitis and may be caused by viruses, bacteria, mycobacteria, rickettsia and rarely by toxoplasma. Viral infections are most common and important cause of encephalitis. JE and Dengue are more prevalent in South East Asia[1]. As a part of efforts to control JE the World Health Organization (WHO) is providing a set of standards for JE surveillance, which require the identification of patients with AES.[2,3]

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According to clinical case definition by WHO, AES is defined as acute onset of fever and a change in mental status including symptoms such as confusion, disorientation, or inability to talk and/ or new onset of seizures excluding febrile convulsions in a person of any age at any time of year.[4] Cerebral malaria and non infectious causes of encephalopathy are required to be excluded while considering AES. Confirmation of diagnosis of JE is usually done by JE specific titers of IgM antibodies in serum and or in CSF during acute illness of suspected AES case.[2]

JE is caused by a zoonotic flavivirus which is one of the common causes of AES. It is difficult to eradicate

JE because it is transmitted from natural reservoirs like pigs, waddling birds which are important amplifying hosts and man is involved as an accidental host. JE has been controlled effectively through vaccination programs in several Asian countries like Japan, Korea, China and Thailand.[5] Culex tritaeniorhyncus is the principle vector of JE in Nepal, as the species is abundantly found in the rice field ecosystem of the endemic areas during the transmission season. Increase in JE cases is observed after the rainy season peaking between August and September.[6]

JE was first observed in Nepal in 1978 as an epidemic in Rupandehi district of the Western Development Region and Morang of eastern region.[6] Between 1978 and 2004 around 27000 cases reported with approximately 5000 deaths. From 2004 to 2006, 1323 cases of JE were confirmed in lab. Total 24 Tarai districts are endemic with CFR ranging from 5-29% with 10% as an average. Average case fatality in all ages is about 20% in Nepal.[6] CFR and morbidity due to JE can be reduced significantly by early diagnosis and appropriate supportive care.[5]

Present study is carried out with the objective to evaluate the clinical profile of hospitalized pediatric AES cases, to determine the prevalence and outcome of meningitis or encephalitis presentation of AES and to document what proportion of these cases are serology proven JE with case fatality.

Materials and methods

This study is carried out in children with clinical diagnosis of AES admitted in pediatric wards of College of Medical Sciences Teaching Hospital, Bharatpur, Nepal for 2 years from January 2007 to December 2008.

This is a retrospective descriptive study done on 61 patients up to 15 years of age diagnosed as AES according to WHO case definition admitted during two years. Case records of these patients were analyzed in detail and data recorded for history, examination, investigation and outcome. Patients were categorized on the basis of predominant clinico-investigational picture suggestive of meningitis or encephalitis.

Surveillance of JE is being done by WHO in endemic areas through detection of JE IgM antibodies in acute stage of AES patients either in serum or serum and CSF samples. College of medical sciences-teaching hospital is one of the JE surveillance center recognized by WHO, Nepal. Blood and or CSF samples of all clinical AES cases from our institution are routinely being sent to WHO program for immunization preventable diseases (WHO IPD) field office, Hetauda as per requirement suggested by WHO for confirmation by JE IgM (ELISA) which is processed at Nepal public health laboratory Teku, Kathmandu. Reports of these cases were correlated later with respective patient when received through WHO IPD field office, Hetauda.

All pediatric patients upto 15 years of age fulfilling the standard WHO case definition of AES as mentioned above were included in the study. Exclusion criteria included patients presented like AES picture but with clinico-investigational diagnosis confirmative of cerebral malaria, Reye syndrome or other non infectious encephalopathy. Statistical significance was analyzed by deriving p value.

Results

There were 61 cases of AES pediatric patients up to 15 years of age during two years of study period fulfilling the WHO definition. Profile of these cases is shown in table-1. Age distribution of these cases was 14, 16 and 31 in less than 1 year, 1 to 5 year and 5 to

15 years respectively. Male and female patients were 33 and 28 and this was statistically insignificant ($p>0.05$, Table-2). Meningitis and encephalitis cases were 29 and 32 respectively. Encephalitis was documented significantly more in male as compared to female ($p<0.015$) whereas meningitis was more commonly observed in female (Table-3). Out of total 61 cases of AES, 30 were discharged home, 13 expired, 9 were referred most often on request and another 9 left against medical advice (LAMA). Statistically significant patients of meningitis ($p<0.0003$) and encephalitis ($p<0.04$) were discharged home as compared to LAMA, referred or expired (Table-4). Excluding LAMA and referred cases there was statistically less mortality in meningitis ($p<0.05$) as compared to high mortality in encephalitis patients (Table-5).

Serology for JE IgM (ELISA) was positive in 11 cases as per documented reports received from WHO field office out of 61 total cases of AES. Most of these patients (72.7%) were from Nawalparasi (8 out of 11) and one each from Chitwan, Tanahu and Makwanpur districts. In year 2007, one, 3 and 4 cases were documented in August, September and November respectively, whereas in 2008, 2 cases occurred in July and 1 in August. IgM seropositive cases consisted of 18% of all AES patients (Table-6). Among 11 seropositive cases male patients were 7 (63.6%) as compared to 4 (36.3%) female cases. No JE seropositive case was found in less than 1 year, only 2 (18.1%) cases belonged to 1 to 5 years age group and maximum 9 (81.8%) patients were between 5 to 15 years of age. Table-6 shows that statistically highly significant less number of patients had positive JE IgM serology in year 2008 ($p<0.00004$) as compared to year 2007 ($p<0.0157$). Among those 11 cases positive for JE IgM, 6 (54.5%) were discharged home, 2 (18.1%) were taken LAMA, none was referred and remaining 3 (27.2%) expired in the hospital.

Discussion

The JE is the single largest cause of viral encephalitis in the world[7]. To monitor JE surveillance, WHO has given clinical case definition of AES so that these cases are subjected for confirmative diagnosis by IgM captured ELISA in blood and or CSF and preventive and supportive interventions can be planned and implemented in endemic or epidemic situations.

JE is a significant health problem throughout Asia. Epidemics of JE are documented in Southeast Asia and most of the Indian subcontinent. In 2005, there was a severe epidemic of JE in the Eastern Uttar Pradesh, as well as in the adjoining areas of the neighboring state of Bihar and in Nepal.[7] The clinical disease presents with a prodromal stage, an acute encephalitic stage with varying grades of coma, convulsions and neurological deficits with high mortality or convalescent stage of recovery often with sequelae.

Clinical profile of AES patients in this study (Table-1) included vomiting, seizures, Glasgow coma scale (GCS) <8, meningeal irritation signs, neurological deficit in 49.1%, 90.1%, 29.5%, 49.1% and 16.2% respectively. Study done by Gupta N et al. observed vomiting in 41.4%, seizures in 79.3%, altered sensorium in 51.7%, signs of meningeal irritation in 17.2% and neurological deficit in 34.5% of their cases in the study done in hospitalized patients suspected of JE.[8] Some of these findings are comparable with present study. In another study done to determine the etiology of febrile encephalopathy by Rayamajhi et al. seizures was documented in 58% of cases which is less than our data.[9] Kumar et al. described vomiting in 6.5%,

meningeal signs in 35.1%, GCS <7 in 44.1%, extrapyramidal features in 31.1% and convulsions in 98.7% in hospitalized patients during JE epidemic in 2005 which occurred in Eastern Uttar Pradesh and adjoining areas of India. These all patients were IgM positive for JE.[7] Differences in clinical picture may be variable depending on various factors like sample size, demographic and epidemiological differences as well as study objective including whether done entirely on encephalitis, investigation of JE epidemic or as per WHO case definition of AES surveillance.

Prevalence of meningitis and encephalitis (Table-3) was 47.5% and 52.4% respectively among 61 cases of AES. Prevalence of JE patients presenting with encephalitis form ranged between 60 to75% and presenting with meningitis form consisted up to 5 to 10% cases.[10] Though these data cannot be compared with our observations which were covering all patients of AES, whereas the data in the reference cited above are for JE cases but still this suggest that patients may present in either way.

Number of AES patients discharged home (58.6%) was significantly more in meningitis (total 29) group (Table-4, p<0.0003) as compared to LAMA (17.2%), referred (17.2%) or expired (6.8%). Out of 32 cases of AES diagnosed as encephalitis 40.6% were discharged home, 12.5% taken LAMA, 12.5% referred and 34.3% patients expired (Table-4, p<0.41). High mortality in this group is consistent with universal observations of more number of deaths in encephalitis including JE.

Encephalitis in this study was statistically more frequent in 2007 and meningitis was more common in 2008 (Table-3, p<0.015). There was significantly less number JE IgM positive cases documented in 2008 (Table-6, p<0.00004) as compared to 2007 (Table-6, p<0.0157). Less number of JE IgM positive cases (3, 9.3%) in the year 2008 as compared to 2007 (8, 27.5%, Table-6) may be because of the fact that effective active immunization campaign involving our institution also by WHO IPD with SA14-14-2 vaccine to all children up to 15 years of age before rainy season in 2008 was undertaken in JE endemic areas identified based on surveillance done in 2007.

In this study most of the cases were confined to Nawalparasi district and occurred after rainy season in September and November in 2007 and July and August in 2008. Other studies also documented prevalence of disease during these months[8,11]. This is because of increase mosquito density during post monsoon period.

Among 11 seropositive cases 7 (63.6%) were male as compared to 4 (36.3%) female patients. Similar trend was also observed in other studies.[9,11] This may be attributed partly because male children are more likely to go out doors or to agriculture area where mosquito vector of the disease is abundant. Most often affected (81.8%) children were between 5 to 15 years of age in the present study which is more or less comparable to other studies.[8,9] This may be correlated to more ambulation in this age group like playing outdoors, going to school or agriculture rice fields predisposing them to vector mosquito bite.

After excluding LAMA and referred cases there were 9 patients seropositive for JE IgM who stayed in hospital till final outcome. Out of these 6 were discharged home whereas 3 died in the institution during two years of study period. Out of those 6 patients who survived 4 were asymptomatic, 1 developed motor deficit with extrapyramidal features and another one had dysphasia on discharge. CFR is the number of deaths/ number of cases diagnosed per year.[12] CFR in

this study was 16.6%. CFR due to JE in Nepal ranged from 9.8% to 46.3% from 1978 to 2003. During recent years CFR has declined and contained below 20% which is comparable to this study.[6] CFR according to the study conducted over wide geographical area covering South Asia, Southeast Asia, China, Pacific Rim and North Australia was between 20-30%.[10] Other studies reported CFR for JE as 8.3% by Rayamajhi A et al. and 12.5% by Shrestha SR et al., which is less than our study.[9,11] These differences may be due to severity of disease at presentation, delay in referral, different geographical and epidemiological factors.

Conclusions

JE confirmed by JE IgM serology contributed to significant cases of AES in children up to 15 years of age. JE is endemic in catchment region of this institution. Male were found to be at more risk for JE and significant number of patients were between 5 to 15 years. CFR for JE in this institution is comparable to global results. JE has significant morbidity and mortality which can be prevented by highly effective live attenuated single dose vaccination or other preventive measures. Sequelae and mortality can be reduced if patients are referred in time for supportive interventions at proper place.

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Table-1: Profile of Acute Encephalitis Syndrome (AES) cases (61):

Feature	**Number (%)**
Fever	61(100%)
Altered Sensorium	61(100%)
Vomiting	30(49.1%)
Headache/ Excessive cry	27(44.2%)
Seizures	55(90.1%)
Glasgow Coma Scale (GCS) < 8	18(29.5%)
Extrapyramidal features	8(13.1%)
Signs of Meningeal Irritation	30(49.1%)
Neurological deficit	10(16.2%)
Fundoscopy	
Normal	47(77%)
Suggestive of papilledema	2(3.2%)
Not required (anterior fontanel was open and flat)	12(19.6%)
CSF	
Suggestive of Bacterial meningitis (Cell counts/ Biochemistry/Gram stain or C/S)	25(40.9%)
Suggestive of viral Meningitis/ Encephalitis (Cell counts/Biochemistry/Neg. Gram stain/Sterile C/S)	22(36%)
Normal CSF/ Refused for Lumber puncture	14(22.9%)

Table-2: Distribution of AES cases According to Age, Sex and Year:

Age	**2007 (AES 29)**		**2008 (AES 32)**		**2007 & 2008**		**Total (61)**
	Male	Female	Male	Female	Male	Female	
<1 yr	4(13.7%)	2 (6.8%)	6 (18.7%)	2 (6.2%)	10	4	14(22.9%)
1 to 5 yr	2 (6.8%)	3 (10.3%)	7 (21.8%)	4 (12.5%)	9	7	16(26.2%)
5 to15 yr	8(27.5%)	10(34.4%)	6 (18.7%)	7 (21.8%)	14	17	31(50.8%)
Total	14(48%)	15(51.7%)	19(59.3%)	13(40.6%)	33	28	61
p value	p >0.05		p >0.05				

Table-3: Distribution of total cases of Meningitis / Encephalitis according to Sex in 2 yrs

Diagnosis	**2007 and 2008**	**Total (AES)**	
	Male (33, 54%)	Female (28, 46%)	61
Meningitis	11 (33.3%)	18 (64.2%)	29 (47.5%)
Encephalitis	22 (66.6%)	10 (35.7%)	32 (52.4%)
p value	p < 0.015		

Table-4: Outcome of Encephalitis/ Meningitis (AES) cases in 2 years

Diagnosis	**Encephalitis (32, 52.4%)**	**Meningitis (29, 47.5%)**	**AES (61)**
Discharged	13 (40.6%)	17 (58.6%)	30 (49.1%)
LAMA	4 (12.5%)	5 (17.2%)	9 (14.7%)
Referred	4 (12.5%)	5 (17.2%)	9 (14.7%)
Expired	11 (34.3%)	2 (6.8%)	13 (21.3%)
p value	p <0.41	p <0.0003	p <0.0001

Table-5: Outcome of Encephalitis/ Meningitis (AES) excluding LAMA/ Referred cases

Diagnosis	**Encephalitis (24, 55.8%)**	**Meningitis (19, 44.1%)**	**Total (43)**
Discharged	13 (54.1%)	17 (89.4%)	30 (69.7%)
Expired	11 (45.8%)	2 (10.5%)	13 (30.2%)
p value	p>0.05	p<0.05	43

Table-6: AES cases according to Serology for JE IgM

Year	**JE IgM Positive**	**JE IgM Negative**	**Total AES (61)**	**p value**
2007	8 (27.5%)	21 (72.4%)	29 (47.5%)	P<0.0157
2008	3 (9.3%)	29 (90.6%)	32 (52.4%)	P<0.00004
2007-08	11 (18%)	50 (81.9%)	61	