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Original Article

Study of acute viral meningoencephalitis in children in sub-Himalayan Tarai region: Clinico-epidemiological, etiological, and imaging profile

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Abstract

Introduction: Sub-Himalayan Tarai region of India is an endemic area for viral meningoencephalitis where rising trend of disease prevalence has been observed over last 3 years. **Objective:** This study was conducted to find the viral etiology, clinical profile, and epidemiology of meningoencephalitis cases and correlate them with imaging results. **Materials and Methods:** A hospital-based prospective observational study was conducted over a period of 1-year (1st January-31st December 2011). Children aged 1 month to 12 years admitted with the diagnosis of viral meningoencephalitis were included in the study. Cerebrospinal fluid and serum immunoglobulin enzyme-linked immunosorbent assay was done for herpes simplex 1 virus, measles, mumps, rubella, varicella, Japanese encephalitis, dengue, and human immunodeficiency virus, on all suspected patients. Neuroimaging (Magnetic resonance imaging brain or computed tomography head) was also performed. **Results:** Mean age was 5.2±3.46 years (range 1 month to 12 years) with a Male:Female ratio of 1.8:1. A maximum number of cases was recorded in monsoon. Paramyxovirus (mumps) was the most common detected virus followed by Japanese encephalitis cases. Case fatality rate for Japanese encephalitis was 54.55% (95% confidence interval 39.54-69.56), and the majority of the deaths occurred in the age group of 3-7 years (38.46%). At 6 months follow-up, 71.4% were absolutely symptom free, while rest had weakness of all limbs, mental retardation, or aphasia. **Conclusion:** Significant encephalitis is prevalent in all districts of North Bengal. Most prevalent are JE and mumps which are vaccine preventable.

Key words: *Mumps, Japanese encephalitis, Viral meningoencephalitis*

Viral meningoencephalitis is one of the most important causes of acute encephalitis syndrome (AES). AES is characterized by the acute onset of fever and change in the mental status (such as confusion, disorientation, coma, or inability to talk) and/or new onset of seizures (excluding simple febrile seizures) in a person of any age, at any time of the year [1]. Dengue and Japanese encephalitis are more prevalent in South East Asia and Indian subcontinent than the rest of the world [2].

In the tropics of sub-Himalayan Tarai region of India, a considerable number of children are diagnosed with AES throughout the year. Previous studies conducted on viral encephalitis in these regions have shown the rising trend of disease prevalence in the last 3 years [3,4]. We conducted this study to find the viral etiological profile of children of sub-Himalayan Tarai region admitted with viral meningoencephalitis and to correlate the clinical presentations with the epidemiological and the imaging results.

MATERIALS AND METHODS

Our institute, a government tertiary care rural medical college of West Bengal caters the referred patients from the sub-Himalayan tropical Tarai region. A hospital-based prospective observational study was conducted over a period of 1-year 1st January-31st December 2011. Institutional Ethics Committee approval was obtained before starting the study. The study population consisted of children aged 1 month-12 years admitted with features of acute meningoencephalitis. Written consent was obtained from the parents or legal guardians of the eligible patients before recruitment into the study.

The clinical diagnosis of acute meningoencephalitis was made in presence of all of the following: (i) fever, (ii) altered sensorium for >12 h with/without motor or sensory deficit or convulsion, and (iii) total duration of illness at the time of admission 1 week or less [5]. Children who presented with other causes of febrile encephalopathy such as pyogenic and tubercular meningitis, cerebral malaria, dyselectrolytemia, intracranial

space occupying lesion (ICSOL), Reye's syndrome, enteric fever, and hepatic encephalopathy were excluded from the study.

All the relevant clinical findings on admission and the investigations were recorded in pre-structured proforma. A careful record of the patients' course in the ward was kept. Routine investigations such as complete hemogram, electrolytes, blood glucose, renal function tests, liver function tests, malarial parasites and antigens, blood culture and sensitivity (BACTEC), cerebrospinal fluid (CSF) studies (cell type, cell count, protein, sugar, gram stain, culture) were done.

The patients were suspected to have viral meningoencephalitis in the absence of bacteria on direct examination of CSF or negative blood/CSF culture with or without CSF pleocytosis with lymphocytic predominance. CSF and serum immunoglobulin (IgM) enzyme-linked immunosorbent assay (ELISA) for (1) herpes simplex 1, (2) measles, (3) mumps, (4) rubella, (5) varicella, (6) Japanese encephalitis (JE), (7) dengue, and (8) Human immunodeficiency virus (HIV) were done on all suspected patients. Isolation of viruses were done for detection of specific nucleic acid by polymerase chain reaction (PCR) replacing the direct inoculation of specimens into cell lines done previously. Our collaborating laboratories were a Department of Microbiology of our institute and Department of Virology, School of Tropical Medicine, Kolkata, National Institute of Cholera and Enteric Diseases.

Computed tomography scan/magnetic resonance imaging (MRI) brain was done to rule out ICSOL and to find out specific changes of viral encephalitis. For radiological diagnosis, help was taken from the Department of Radiodiagnosis of our institute. Based on the clinical features and investigations, the patients diagnosed as pyogenic meningitis, cerebral malaria, ICSOL, metabolic disorders were excluded. Diagnosis of viral encephalitis was made in the presence of any of the following criteria:

i. Detection of virus-specific IgM antibodies in CSF and/or serum
ii. More than four-fold rise in serum antibody titers by ELISA
iii. Isolation of virus in CSF.

All patients were treated by supportive care like intravenous fluid, correction of electrolytes, decongestive measures to reduce intracranial tension, ionotropes in hemodynamic instability, maintenance of blood glucose, anticonvulsants, antibiotics, antiviral, physiatric management as and when needed. Follow-up of all the discharged cases were planned over next 6 months. During follow-up, thorough neurological evaluation was done to assess the patients for residual neurological sequelae. If necessary, repeat MRI brain was also done to assess the radiological improvements.

All previous years' data had been collected from our record keeping section and compared with present year's data. Incidence of viral encephalitis in each season, i.e. summer (March, April, May), monsoon (June, July, August), autumn (September, October, November), and Winter (December, January, February) of 2009, 2010, and 2011 were compared to detect the seasonal trends.

Data have been summarized by descriptive studies, i.e., mean and standard deviation for numerical variables (also median where appropriate) and counts and percentages for categorical variables. Categorical variables were compared between groups by Chi-square test or Fisher's exact test as appropriate. $p<0.05$ was considered as statistically significant. SPSS version 17.0 software was used for statistical analysis.

RESULT

Total 161 patients were clinically diagnosed as viral meningoencephalitis and were recruited in the study. Mean age was 5.20±3.46 years (range 1 month-12 years) with Male:Female ratio of 1.8:1 (Table 1). There was no significant difference between male and female patients (p=0.343). The majority of the cases were from North Bengal, e.g., Jalpaiguri (23.60%) followed by Maldah (21.74%) and Darjeeling (21.12). Uttar and Dakshin Dinajpur, Cooch Bihar, and Murshidabad accounted for 29.8% of the cases while 3.73% cases were referred from outside such as Bihar and Nepal. Comparing encephalitis data over last 3 years, it was seen that the number of cases had gradually increased with maximum occurrence in the monsoon season (Fig. 1). There was no significant seasonal trend in 2011 (Chi-square 1.494, df=1, p=0.222).

All 161 cases had a fever and altered sensorium at the time of presentation. Glasgow coma score was <8 in 46 cases. 40.37% cases had associated seizure in the form of generalized tonic-clonic seizure (90%) or focal seizure (10%). Seizure occurred mostly on the 2nd-6th day of illness. Signs of meningeal irritation

Table 1: Age and sex-wise distribution of cases

Age group (year)	Male	Female	Total (%)
1 month-≤3	42	22	64 (39.75)
>3-≤7	36	15	51 (31.68)
>7-12	26	20	46 (28.57)
Total (%)	104 (64.6)	57 (35.4)	161 (100)

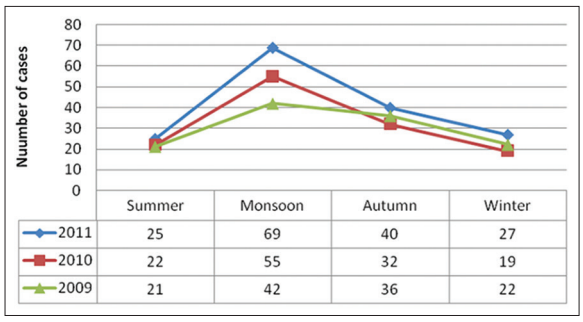

Figure 1: Viral encephalitis trend over last 3 years

were found in 40.37% cases. Hepatomegaly (54, 33.54%), splenomegaly (17, 10.56%), pyramidal signs (17, 10.56%), extra pyramidal signs like tremor, dystonia, choreiform movements (42, 26.09%), acute left ventricular failure (2, 1.24%) were other associated features. No case presented with rash, parotitis or cranial nerve involvement.

Among 161 clinically suspected cases, definite viral etiology was detected in 48 cases (Table 2). Exact viral etiology could not be determined in the rest of the (113) cases; however, clinical profile, lymphocytic pleocytosis of CSF and course of illness pointed toward the diagnosis of viral encephalitis. Mean CSF cell count was 79.4±29.23 cells; sugar was 65.5±13.64 mg/dl, and protein was 231.7±67.65 mg/dl. Maximum deaths were in the month of August (12, 30.77%). The highest case fatality rate was observed in HIV (75, confidence index [CI] 59.69-90.31) followed by measles (66.67, CI 39.46-93.89) and JE (54.55, CI 39.54-69.56) infection.

MRI of the brain could be done in 56 cases. Of the rest, 52 cases were very ill, 29 cases died early, and 24 cases could not afford it. MRI findings were abnormal in 21 cases. Three of them showed hyperintensity in T2W1, and fluid-attenuated inversion recovery (FLAIR) restricted diffusion involving basal ganglia, thalamus, and brainstem. All three cases were confirmed as JE. 11 cases had the hyper intensity of cortex in T2W1 and FLAIR, suggesting cerebral infarct (herpes = 4, unspecified = 7). Rest seven cases had dilated ventricular system with cortical atrophy (unspecified = 7).

Of 161 patients, 39 died, 112 were discharged, and 10 left against medical advice. Time of death varied from 2nd to 30th day of illness with a median of the 5th day. The majority of the deaths was in the age group of 3-7 years (38.46%) (p=0.008), followed by age group of 7-12 years (35.8%) and 1 month to 3 years (25.64%). Mortality rate was twice in male as compared to females (71.8% vs. 28.2%) which was statistically insignificant (p=0.117, Chi-square =4.293, df=2) (Table 3).

Table 2: Viral etiology

Viral etiology	Number	Death	Case fatality rate	CI (95%)
Unspecified viral infection	113	23	20.35	16.57-24.13
HIV	8	6	75	59.69-90.31
Mumps	17	0	0	-
Japanese encephalitis	11	6	54.55	39.54-69.56
Herpes	8	2	25	9.69-40.31
Measles	3	2	66.67	39.46-93.89
Rubella	1	0	0	-

CI: Confidence interval, HIV: Human immunodeficiency virus

Out of 112 cases, 80 (71.4%) cases were discharged without any squeal, 14 (12.5%) had weakness of all limbs; mental sub normality was present in 10 cases, hemiparesis in 5, and weakness of limbs with aphasia in 3 cases. Follow-up was done for 6 months. Eight cases were lost in follow-up. On follow-up at 6 months, cases with mumps encephalitis were found to be absolutely normal. Limb weakness, decreased scholastic performance, and mental retardation was noted in cases with herpes encephalitis. Two confirmed cases of JE had limb weakness and mental retardation, and two cases had aphasia.

DISCUSSION

The incidence of AES ranges from 10.5 to 13.8 per 100,000 children as concluded from various prospective studies from the Western world [6]. Worldwide the commonest cause of viral encephalitis in children is Japanese encephalitis. Every year, there are approximately 50,000 cases of JE and causes death in 10,000 [7,8]. The incidence of JE is gradually increasing in South East Asia and Indian subcontinent over the last few years [9-14]. Its incidence in the tropical countries is about 2-15 per 100,000 [12,15,16]. In India, the largest epidemic outbreak in last three decades occurred in Gorakhpur, Uttar Pradesh through November 2005 killing 1344 people [17]. In our study, mumps (Paramyxovirus) was the most common detected virus followed by Japanese encephalitis cases.

Neonates were excluded from our study because frequently they have conditions like hypoxic ischaemic encephalopathy, metabolic disorders, septicaemia in which encephalopathy is only one aspect and not a distinct clinical entity [18]. The upper age limit of 12 years was taken as most hospitals in India including ours admit patients in the wards till that age. Only patients with continuing alteration of consciousness of more than 12 hours were included to exclude febrile convulsions and aseptic meningitis.

In our series, male were almost twice in number compared to females (104 vs. 57). This was similar to the results of other studies conducted in India [5,19,20]. This male preponderance could be explained by the male child leading a more active outdoor life including helping in agricultural fields, where the chances of getting bitten by flavivirus-infected culex tritaeniorhyncus/Vishnui is more in the rice field ecosystem of the endemic areas during the transmission season.

The seasonal trend showed the maximal occurrence of cases in the monsoon and post monsoon months which is consistent with the findings of other studies [20-22]. This is because of increased mosquito density during this period. However, no statistically significant difference was seen in the seasonal trend for the year 2011.

In our study, fever and altered sensorium were the presenting complaint in all cases followed by convulsion, meningeal

Table 3: Distribution of death according to age and sex

Age group (year)	Male	Female	Total (%)	Case fatality rate	CI (95%)
1 month-≤3	8	2	10 (25.64)	15.62	6.54-24.7
>3-≤7	14	1	15 (38.46)	29.41	16.64-42.16
>7-12	6	8	14 (35.8)	30.43	23.65-37.21
Total (%)	28 (71.8)	11 (28.2)	39 (100)		

CI: Confidence index

signs, extrapyramidal signs, and pyramidal signs. Khinchi et al.[20] reported convulsion in 90.1%, meningeal signs in 49.1%, extrapyramidal signs in 13.1%, and neurological deficit in 16.2%. Karmakar et al.[5] in their study conducted in Delhi showed convulsions (70.17%) and meningeal signs (59.64%) as the most common clinical features. Our study also showed the absence of rash in measles and parotitis in mumps in a few cases. These findings have been reported previously by Sherman et al. [23] Wairagkar et al. [24] and Xu U et al. [25] showing rubella encephalitis, acute measles encephalitis, and mumps encephalitis, respectively, without rashes or parotitis.

In our study, exact viral etiology was found in only 29.8% cases; the commonest being mumps (10.6%) and rest (70.2%) had "unspecified" viral etiology. In a large UK study [26] of 700 cases, "unspecified" viruses were the commonest cause (60%) followed by herpes (24%) infection. It is hoped that with more widespread use of PCR tests the number of "unspecified" viruses will decrease over time in India and worldwide [26,27]. A viral agent was discovered in 26-65% of suspected cases in other similar studies [25,28-32]. In India, most of the studies were conducted after an outbreak which invites selection bias regarding the etiology. Karmakar et al.[5] showed that enterovirus 71 as the most common cause (35.1%) in Delhi while Kumar et al.[28] showed JE as the commonest etiology (23%).

MRI brain showed abnormalities in the basal ganglia, thalamus, brainstem, and cortex as seen by other researchers [5,26,27] Davison et al. [26] considered MRI diagnostic but Steiner et al. [27] suggested newer modalities such as gradient-echo imaging for detecting small areas of hemorrhage and diffusion weighted imaging to distinguish old from new insults. CT is recommended only as a screening examination, or when MRI is not available [27].

Case fatality rate was 25.15% in our study which is comparable to other studies with reported mortality rates ranging from 20 to 30% [26,33]. A recent study from Nepal reported fatality rate below 20% [34]. These differences may be due to the severity of disease at presentation, delay in referral, and different geo-epidemiological factors. Sequelae such as quadriparesis, hemiparesis, mental retardation, and aphasia were present in 23% of the cases. Other studies had differing rates of sequelae which can be explained by the aforesaid reasons.

Limitation of our study is that it was a hospital-based study catering patients from a limited geographical area, and there might be a component of referral bias. We need a community-based serosurveillance program to draw a conclusion to the presence of a particular virus in the community.

CONCLUSION

We attempted to give a clinico-etiological and radiological profile of acute meningoencephalitis in North Bengal and surrounding areas in light of newer investigative modalities such as PCR and MRI. Significant encephalitis was found to be prevalent in all districts of North Bengal during monsoon season. Extensive immunization coverage against Mumps and JE viruses should be attempted to prevent meningoencephalitis and subsequent mortality and morbidity.

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