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Research Article

Viral Etiology in Acute Encephalitis Syndrome in North Indian Children

Arunkumar M[1], Anju Aggarwal[2*], Aaradhana Singh[3], Rajeev Thakur[4], NP Singh[5], Prerna Batra[6], Rajeev Malhotra[7]

[1]Third Year Student, Department of Pediatrics, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India

[2]Pediatrics, FIAP, Director Professor, Department of Pediatrics, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India

[3]Pediatrics, Associate Professor, Department of Pediatrics, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India

[4]Professor and Head, Department of Microbiology, Institute of Human Behaviour and Allied Sciences, Delhi, India

[5]Professor and Head, Department of Microbiology, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India

[6]Pediatrics, Professor Pediatrics, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India

[7]Scientist (Statistics), Delhi Cancer Registry, Dr. BR Ambedkar Institute Rotatory Cancer Hospital, AIIMS, Delhi, India

[*]**Corresponding Author:** Anju Aggarwal, MD Pediatrics, FIAP, Director Professor, Department of Pediatrics, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India;
Email: aanju67@gmail.com

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Abstract

Background and Objective: Acute Encephalitis Syndrome (AES) leads to significant mortality and morbidity in children. This study was undertaken to identify the viral causes of AES and its correlation with clinicodemographic profile.

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Methods: This cross-sectional study included 100 children aged 1 to 12 years presenting with fever of <14 days duration 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) [1]. Cerebrospinal Fluid (CSF) was collected aseptically by lumbar puncture for biochemical and cytological analysis, and for bacteriological culture. Multiplex PCR for the viruses HSV1, HSV2, Varicella zoster virus, Enterovirus, Mumps and Parecho virus was carried out. Serology for Japanese Encephalitis (JE) was done in blood and CSF by ELISA method. Dengue NS1 antigen and IgM ELISA was carried out in both blood and CSF samples. Serum IgM antibody for scrub typhus was done by ELISA method.

Results: Out of 100 children viral cause was detected in 21 patients (Japanese encephalitis -16, Dengue - 4, Varicella zoster virus, Enterovirus and Mumps virus - 1 each). Serum IgM ELISA for scrub typhus was positive in 6 patients. Multiple viral etiology was seen in 2 patients. Mortality was significantly more in females ($p=0.021$), GCS <8 ($p <0.001$). Mortality was significantly more with higher CSF neutrophils and higher proteins ($p<0.05$).

Interpretation and Conclusion: This study concludes that viral causes specially JE contributed in AES in North India. Hence viral pathogens including JE needs to be considered as one of major causative agents while treating patients of AES and further emphasis has to be given for JE vaccination in this region.

Keywords

AES; Cerebrospinal Fluid; Japanese Encephalitis; Vaccine; Viral Etiology

Abbreviations

AES: Acute Encephalitis Syndrome; COVID: Corona Virus Disease of 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Corona Virus 2; PMN: Polymorphonuclear; CSF: Cerebrospinal Fluid

Introduction

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) [1]. AES is caused by various agents like bacteria, fungi and parasite, the viruses are implicated to be the most important cause [2]. Global incidence varies between

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studies but is generally between 3.5 and 7.4 per 100,000 patient years [3]. India contributes for the large number of AES cases. Causative organisms vary from place to place. Viruses are important cause of AES in India. Common viruses from north India are HSV-1, HSV-2, JE and Dengue virus [4]. The viral agents causing AES vary according to different geographical areas (HSV in Rajasthan, JE in UP) [4]. However there are limited number of studies regarding the incidence, etiology and clinical profile of Acute Encephalitis Syndrome (AES) in Indian subcontinent. Hence this study was planned to find viral etiology in children with AES and correlate it with clinic-demographic profile.

Material and Methods

It was a cross-sectional study, conducted in department of Pediatrics University College of medical sciences and GTB hospital, Delhi and Department of Microbiology, IHBAS, Delhi. An approval from the ethics committee was obtained.

According to the study done by Kumar R, et al., viral etiology was found in 57.58% and another study by Tiwari JK, et al., had a viral etiology in of 41.10% (in children) [6,7]. Hence an average of 50% prevalence is considered and a sample size of 100 is calculated with an estimated true proportion rate (R) of 0.50 at a confidence level of 95% assuming desired precision rate of 20% (Relative error).

Children of age group 1-12 year who were admitted to the pediatric emergency with fever of <14 days duration 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) were enrolled. CSF examination showing Polymorphonuclear (PMN) leukocytosis (>80%) or protein >40 mg/dl, were considered as bacterial meningitis [5]. CSF picture showing predominant lymphocytes plus positive Tuberculin skin test or radiological features suggestive of tuberculosis will be considered were considered as tubercular etiology. Those in whom viral serology was positive were confirmed viral.

Written informed consent was taken from parent/ guardian of each subject. Patients were treated as per standard guidelines followed in the hospital. Each study subject was evaluated by detailed history and examination. Patients demographic, clinical and investigation details were recorded. Children with dyselectrolytemia and children with developmental delay and neurological regression were excluded from the study.

All patients were treated as per standard protocol of the hospital, initial treatment with ceftriaxone, vancomycin and acyclovir. Patient also received intravenous fluid, antiepileptic and supportive drugs as required. Child was followed up till discharge or death.

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Cerebrospinal Fluid (CSF) sample was collected within 24 hours of admission, aseptically by lumbar puncture in a sterile leak proof container sent for biochemical (sugar and protein), cytological (TLC and DLC) and microbiological (gram stain, AFB stain, bacterial culture) examination. In suspected viral etiology (all cases in present) 1 ml of CSF sample was transported to IHBAS and multiplex PCR was performed on real time platform (ABI 7500 platform) - Fast track diagnostics viral meningitis kit, for the viruses HSV1, HSV2, Varicella zoster virus, Enterovirus, Mumps and Parechovirus. Serology for JE was done in blood and CSF by IgM ELISA method. Dengue NS1 antigen and IgM ELISA was carried out in both blood and CSF samples. Serum IgM antibody for scrub typhus was done by ELISA method.

Results

A total of 100 children (47 females, 53 males) were enrolled. We confirmed viral etiology in 21 subjects (Table 1). IgM ELISA for Scrub typhus was positive in 6 cases. Tubercular meningitis was diagnosed in 4 cases. Multiple etiologies like Scrub typhus with JE, Tubercular meningitis with JE was detected in 1 patient each.

The clinicodemographic profile of study subjects and its effect on outcome (discharge and expiry) is depicted in Table 2. Fever was the most common presenting feature (99%) followed by seizure (70%), vomiting (42%) and headache (20%). 8 patients had rash and 2 patients had history of ear discharge. Any of the clinical features were not very specific for differentiating viral and other non-viral causes of Acute encephalitis syndrome ($P>0.05$). Altered sensorium (n=65) was the most common CNS feature followed by features of meningeal signs (n=43) and abnormal behavior (n=18). Cranial nerve palsy was noted in 5 patients, cerebellar signs in 2 patients and 3 patients had papilledema.

Bacterial etiology was suspected on the basis of clinical profile and CSF findings in 27 patients and culture positivity with CONS (Coagulase Negative *Staphylococcus*) was seen in 1 patient. Bacterial antigens were tested in CSF showed positivity for *Streptococcus pneumonia* in 3 cases.

Neuroimaging was showing features of meningoencephalitis in 12 patients, features of tubercular CNS disease in 4 cases and was apparently normal in others. Leukocytosis was observed in 44% of the patients.

In our study we observed that GCS of <8, presence of neutrophils (IQR=65) and raised protein levels (IQR=74) in CSF were significantly associated with higher mortality rate. There was no significant difference found in mortality rate between viral cause and other causes of acute encephalitic syndrome. No significant relation was found in the clinical features at presentation like seizures, vomiting, headache, abnormal behaviour, altered sensorium and signs of meningeal irritation in viral and other causes of AES.

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Patient clinical profile with respect to etiology is summarized in Table 3. Absence of cells in CSF was significantly associated with viral cause. No significant relation was found with presence of seizure, altered sensorium, signs of meningeal irritation, vomiting and headache.

Virus tested	Numbers
Japanese encephalitis	16
Dengue virus	4
Varicella zoster virus	1
Enterovirus	1
Mumps virus	1
Herpes simplex virus 1	0
Herpes simplex virus 2	0
Parecho virus	0

Table 1: Viral etiology in study subjects.

	Discharge (n=82)	Expiry (n=18)	p-value
Demographic profile			
Age group (in years)			
– 1 to 5 (n=55)	44	11	
– 5 to 8 (n=18)	14	4	0.601
– 8 to 12 (n=27)	24	3	
Sex			
– Female (n=47)	34	13	
– Male (n=53)	48	5	0.021*
Residence			
– Delhi-NCR (n=79)	65	14	1.000
– Outside Delhi (n=21)	17	4	

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Clinical profile			
Seizures – Yes (n=70) – No (n= 30)	 57 25	 13 5	 1.000
GCS – <8 (n=12) – ≥8 (n=88)	 4 78	 8 10	 <0.001*
Altered sensorium – Yes (n=65) – No (n=35)	 51 31	 14 4	 0.279
Signs of meningeal irritation – Yes (n=43) – No (n=57)	 35 47	 8 10	 1.000
Abnormal behaviour – Yes (n=18) – No (n=82)	 17 65	 1 17	 0.182
Vomiting – Yes (n=42) – No (n=58)	 34 48	 8 10	 1.000
*p value <0.05 is considered statistically significant			

Table 2: Effect of clinicodemographic profile on outcome.

	Viral (confirmed +suspected) (n=64)	**Others (bacterial, tubercular, Rickettsial) (n=36)**	**p-value**
Seizures – Yes – No	 46 18	 24 12	 0.652

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Vomiting			
– Yes	30	12	0.211
– No	34	24	
Headache			
– Yes	13	7	1.000
– No	51	29	
Abnormal behavior			
– Yes	15	3	0.101
– No	49	33	
GCS			
– <8	6	6	0.342
– ≥8	58	30	
Altered sensorium			
– Yes	41	24	0.830
– No	23	12	
Neuroimaging findings			
– Normal	46	21	0.581
– Meningoencephalitis	7	5	
Signs of meningeal irritation			
– Yes	25	18	0.302
– No	39	18	
CSF cells			
– Present	28	29	0.001*
– Absent	36	7	
*p value <0.05 is considered statistically significant			

Table 3: Clinical profile with respect to etiology.

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Discussion

The present study was conducted to determine viral etiological profile of acute encephalitis syndrome and its clinicodemographic profile in children of north India. In this study we observed that 21% of cases were having microbiologically confirmed viral etiology. This was similar to the study done by Tiwari JK, et al., from Rajasthan who studied 3088 patients of all age group and viral etiology was confirmed in 22.7% cases [7]. Other studies also documented almost similar percentage of viral causes which includes 17.2 % in study by Rathore SK, et al., from Odisha, 16.3% in study by Tripaty SK, et al., from Odisha, 17% in study by Jain P, et al., from Uttar Pradesh and 14% in study by Goel S, et al., from Delhi [8-11].

Among the confirmed viruses, Japanese encephalitis was the most common virus (n=16) followed by Dengue virus (n=4), Varicella zoster virus (n=1), Enterovirus (n=1), Mumps virus (n=1). This was similar to the study done by Jain P, et al., from Uttar Pradesh in 2011 and 2012 where JE virus (16.2%) was most common followed by Dengue virus (10.8%) [12]. Another study by Jain P, et al., from uttar Pradesh from 2014 to 2016 which showed JE virus (8.3%) as most common viral etiology followed by Dengue virus (7.8%) [10]. Study by Rathore SK, et al., from Odisha in 2011 showed 1.5% cases, study by Kumar R, et al., from Agra in 2015 showed 1.36% cases, study by Goel S, et al., from Delhi in 2015 showed 2% cases of JE respectively [6,8,11].

Other studies had Herpes simplex virus as most common cause. The difference from our studies might be due to geographical difference and the age group of study subjects. As in our study we included the age group 1 to 12 year, whereas most of the other studies included patients of all ages including extremes of ages.

In this study half of the study population was of age group 1 to 5 years. Gender distribution was almost equal between males and females. Male patients were having higher incidence of viral cause compared to female (p=0.039). This was similar to study by Rathore SK, et al., and Jain P, et al. However female patients had significantly higher mortality compared to male patients (p= 0.021) (Table 2) [8,10]. The cause may be due to the preference given to the males in bringing them early to the health care facilities.

In our study we observed that GCS of <8 was associated with high mortality (p=0.001). Presence of neutrophils in the CSF (p= 0.001) and raised protein levels in CSF (p= 0.001) were significantly associated with higher mortality rate. Longer duration of the disease (p= <0.001) and longer duration of hospital stay (p= <0.001) were significantly associated with mortality. There was no significant difference found in mortality rate between viral cause and other causes of acute encephalitic syndrome.

In this study the culture positivity rate of bacterial pathogens was very less. This can be due to prior receiving of antibiotics from outside, less sensitivity of the test and delayed inoculation

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of CSF. This problem can be combated by using nucleic acid amplification tests like PCR, which can detect small amount of DNA independently from the growth of micro-organism causing the disease [13]. The CSF sample has to be transported to laboratory from the procedure site, which increases the transit time. The direct plating of CSF on the culture plate can yield better culture results

When clinical features were compared among children of viral causes with non-viral causes of AES most clinical features were not helpful (P>0.05) (Table 3). Multiple etiology was detected in 4 patients. Japanese encephalitis with Dengue, Japanese encephalitis with tubercular, Japanese encephalitis with Mumps and Japanese encephalitis with Scrub typhus. This is similar to study by Jain P, et al., where mixed infections were found in 12 patients and study by Tiwari JK, et al., which showed multiple etiology in 9 patients [12,7]. Hence in tropical countries endemic diseases and multiple etiologies can be considered.

Japanese encephalitis was the most common viral agent detected. Japanese encephalitis cases had significantly less frequency of PICU (Pediatric Intensive Care Unit) admission compare to other viral cases (p= 0.027).

In our study specific investigations like autoimmune encephalitis couldn't be done due to non-availability of the tests and high cost of the tests. In cases of suspected bacterial and suspected viral where specific etiology couldn't be found, receptor encephalitis has to be considered.

Implications

In this study it was seen that 21% of the patients had confirmed viral etiology and Japanese encephalitis was the most common viral agent. Hence high index of suspicion for viral cause has to be kept in cases of Acute Encephalitis Syndrome. Japanese encephalitis is a vaccine preventable disease. Vaccination for Japanese encephalitis is done under national immunization schedule in only high risk districts of Uttar Pradesh, Tamil Nadu, Andhra Pradesh, Karnataka, Haryana, Bihar and Assam. In our study Japanese Encephalitis was the most common viral agent causing Acute Encephalitis Syndrome in Delhi and surrounding area. Hence vaccination coverage should be considered in Delhi including National capital region.

Conflict of Interest

The authors declare that they have no conflict of interest.

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