Clinico-Etiological Profile of Children with Acute Encephalitis Syndrome- A Prospective Observational Study

Divyashree Venkatachalam Swaminathan, MD* ArunPrasath Thasma Santhanakrishnan, MD** Vinoth Ponnurangam Nagarajan, MD, MRCPCH, FRCPCH, MRCPI, MRCPE** Ramachandran Padmanaban, MD*** Vaishnavi Swaminathan, MD **** Dinesh Kumar Jayapalan, MD **

ABSTRACT

Aim: This study was done to find out the etiological profile and outcome of children admitted with AES in an urban tertiary care centre.

Design: A Prospective observational study

Setting: This study was carried out in an urban tertiary care teaching hospital, Chennai, India between September 2014 and July 2016

Method: Children admitted with clinical criteria of AES were included in the study. Demography, clinical presentation, cerebrospinal fluid analysis, electro encephalography and neuroimaging findings were collected. CSF was tested for IgM antibody against Japanese B encephalitis virus (JE), Varicella-Zoster virus and Dengue virus , Gene-expert for Mycobacterium tuberculosis , Polymerase chain reaction for Herpes simples virus , anti NMDA antibody and bacterial culture. Dengue and scrub typhus serology was done in blood. Children were followed up till discharge/death.

Results: 50 children (male n=22) with AES were recruited. In 31 children (62%), aetiology of AES was identifiable. Dengue was the commonest (14%). Posturing, abnormal spino-motor examination findings, abnormal EEG and neuro- imaging findings were significantly associated with mortality or sequelae. 33 children (66%) recovered well. Mortality rate was 8%, neurological sequelae were seen in 13 children (26%).

Conclusion: With advent of JE vaccine inclusion, dengue encephalitis has become the commonest cause of AES. Emerging diseases like scrub typhus and autoimmune encephalitis also should be considered in the evaluation of AES.

Keywords: Acute encephalitis syndrome, Dengue, Japanese B encephalitis, Scrub typhus

INTRODUCTION

Acute encephalitis is defined as a syndrome of neurological dysfunction caused by inflammation of the brain parenchyma[1]. It is usually identified by clinical features supported by CSF pleocytosis or neuroimaging. For the specific purpose of surveillance of Japanese encephalitis, National Vector Borne Diseases Control Programme (NVBDCP), Directorate General of Health Services, Ministry of Health and Family Welfare, Govt of India, initiated a syndromic surveillance based on the WHO criteria of acute encephalitis syndrome (AES)[2].

In majority of the cases, causative organisms of AES could not be detected[2]. Among the known causes, viruses are the commonest one. But the type of viruses causing AES differ across geographical locations and over time. Influenza virus was the commonest cause in Japan[3,] enterovirus in Italy, Mexico and China[4-6] and Herpes simplex virus in England[7]. In India, like in other countries of Asia, Japanese B encephalitis used to be the commonest virus, but after introduction of JE vaccine, HSV was reported as commonest virus[8]. In another large study of AES from selected states (Uttar Pradesh, West Bengal, and Assam) of India, scrub typhus was as common as JE followed by dengue[9]. Knowledge about the etiological profile and factors predicting outcome is important in the patient management and planning prevention.

AIMS OF THE STUDY

This study was undertaken to find out the profile of AES from children admitted in a medical college hospital from Southern Indian state of Tamil Naidu.

MATERIALS AND METHODS

This was a prospective observational study done in a tertiary care, university teaching hospital between September 2014 and July 2016, after Institutional ethics committee approval. All children aged between 1 month and 18 years, admitted with criteria of Acute encephalitis syndrome (AES) as per NVBDCP 2006 criteria[10] were included in the study after informed consent. AES was defined as per

* Assistant Professor
Department of Paedatric
Chettinad Hospital and Research Institute, India.
** Associate Professor
Department of Paediatrics
Sri Ramachandra Institute of Higher education
India. E-mail: dineshkumar.j@sriramachandra.edu.in
*** Professor, Department of Paediatrics
**** Junior Resident

NVBDCP 2006 adoption of WHO, "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 may include an increase in irritability, somnolence or abnormal behavior greater than that seen with usual febrile illness." Demographic details like age, sex, place of residence and socio-economic status and clinical presentation including symptoms and neurological signs were noted. Complete blood count, renal function tests and serum electrolytes were done. Lumbar puncture was done, and cerebro-spinal fluid (CSF) was sent for cytology, biochemical analysis, bacterial culture and GeneXpert for Mycobaterium tuberculosis (MTb). CSF was analysed for IgM antibody against Japanese encephalitis (JE) and dengue, Polymerase chain reaction (PCR) for Herpes simplex virus (HSV) and Varicella zoster virus (VZV) and antibody against N-methyl D-aspartate receptor (NMDAR) wherever clinically indicated. In addition, serum samples were sent for IgM antibody against JE, dengue and scrub typhus. Magnetic resonance imaging (MRI)/Computed tomography (CT) and Electro encephalography (EEG) were done. All children were treated as per standard protocol. Clinical course and outcome were noted. The risk factors for poor outcome were analysed.

Study Definitions:

- **Bacterial Meningitis:** AES with presence of bacteria in CSF (By Gram stain or bacterial growth) or presence of bacteremia in a child with clinical picture and CSF suggestive of bacterial meningitis.
- **Tuberculous Meningitis**: AES with GeneXpert positive for MTb in CSF.
- **Japanese B Encephalitis**: AES with IgM antibody titre against JE more than 40units, in either serum/CSF.
- **Dengue Encephalitis**: AES with IgM antibody titre more than 18units against dengue, in either serum/CSF.
- **HSV Encephalitis**: AES with positive HSV PCR, in CSF.
- **VZV Encephalitis**: AES with positive IgM antibody against VZV in CSF.
- **NMDA Encephalitis**: AES with positive antibody titre against NMDA receptor, in either serum/CSF.
- **Scrub typhus Encephalitis**: AES with positive IgM antibody titre against scrub typhus in serum.
- **Neurologic Sequelae**: Neurological disability at the time of discharge.

RESULTS

50 children (males, n= 22, 44%) were admitted during the study period as AES. There was no seasonal variation observed for AES occurrence in the 2-year study period. Majority of children belonged to upper lower and lower middle class as per Modified Kuppuswamy classification. Clinical symptoms observed were fever (100%), altered sensorium (100%), seizures (62%), headache (48%), vomiting (48%), neck stiffness (26%), and visual disturbances (12%). Clinical signs observed were low Glasgow coma scale (score <8 in 22%), meningeal signs (32%), cranial nerve involvement (6%), abnormal spino-motor system findings (78%), abnormal posturing (20%) and early papilledema (14%).

18% of cases had leucocytosis in blood count and 8 % had hyponatremia. Dengue serology was positive in 14% of cases and scrub typhus serology was positive in 2 (4%) of cases. Two children (4%) grew Salmonella typhimurium in blood culture.

CSF analysis was done in 49 cases. In one case, as there was brain stem dysfunction, lumbar puncture could not be done, and child expired and was diagnosed as encephalitis of unknown etiology. CSF showed pleocytosis in 23 (46%), elevated protein in 19 (38%) and low sugar in 16 (32%) cases. Gram stain was positive in 5 children (10%) and 3 (6%)grew bacteria in CSF. GeneXpert for MTb was positive in 5 children (10%). Serology for JE, PCR for HSV-1, PCR for HSV-2 and serology for NMDAR antibody was positive in one child (2%) each. EEG was abnormal in 10 (20%) of cases and MRI was abnormal in 22 (44%) of cases.

Final diagnosis was made based on clinical, laboratory and neuro imaging as shown in Table I. In 31 case (62%) children a definitive diagnosis could be made and in 19 cases (38%), a definitive aetiology could not be established. Complications observed in the cases are shown in Table II. Thirty-three children (66%) were discharged normally, 7(14%) were discharged with minimal disability, 3(6%) were discharged with sequelae, 3(6%) were discharged against medical advice without improvement and 4 children (8%) died. Clinical findings

Table 1: Aetiological profile of AES

Diagnosis	Number of patients n=50	Diagnostic criteria
Dengue encephalitis	7(14%)	Positive Dengue Serology
Bacterial meningitis	6(12%)	Bacterial growth in CSF
TB meningitis	5(10%)	GeneXpert positive for MTb
Salmonella typhimurium meningitis	2(4%)	CSF pleocytosis with Salmonella typhimurium growth in Blood culture
Varicella encephalitis(VZV)	1(2%)	CSF PCR positivity
VZV+ Influenza(H3N2) encephalitis#	1(2%)	CSF PCR positivity
HSV 1 encephalitis	1(2%)	CSF PCR positivity
HSV 2 encephalitis	1(2%)	CSF PCR positivity
Japanese encephalitis	1(2%)	CSF PCR positivity
Autoimmune encephalitis	1(2%)	Anti NMDA positivity in serum
Scrub typhus encephalitis	1(2%)	Serology Positivity
Fungal meningitis	1(2%)	Growth in CSF
Rasmussen's encephalitis*	1(2%)	Neuro imaging finding
Atypical GBS	1(2%)	CSF findings plus NCV (nerve conduction velocity)
Hepatitis A with hepatic encephalopathy	1(2%)	Serology positivity
Acute encephalitis of unknown etiology	19(38%)	---

* Diagnosis made on basis of clinical presentation and neuroimaging suggestive unihemispheric brain involvement with normal CSF analysis
# One child with VZV had coexisting H3N2 infection

of posturing and abnormal findings in spino- motor examination were significantly associated with poor outcome. Abnormal findings in EEG and neuroimaging were significantly associated with poor outcome (Table III).

Table 2: Acute complications observed in AES

Complications	Number of patients N=50
MODS	6(12%)
Need for Mechanical ventilation	24(48%)
Dyselectrolytemia*	14(28%)
Respiratory complication #	6(12%)
Secondary sepsis$	4(8%)
Sensory neural hearing loss	1(2%)
Myocardial dysfunction	2(4%)
Shock	7(14%)
Acute kidney injury	4(8%)
Acute liver injury	5(10%)
Hydrocephalus	2(4%)
Neurological disability**	8(16%)
Brainstem dysfunction	3(6%)
Increased intracranial pressure	7(14%)
Status epilepticus	5(10%)

MODS- multiple organ dysfunction syndrome
ARDS- Acute respiratory distress syndrome
** Neurological disability in the form of Quadriplegia (n=4), Right hemiparesis (n=2) paraparesis (n=1), monoparesis (n=1)
*Dyslectrolytemia – Hyponatremia(n=9) and metabolic acidosis(n=10)
# Respiratory complication- ventilation associated pneumonia (n=4); ARDS (n=2)
$ secondary sepsis- blood culture positive sepsis(n=4)

Table 3: Prognostic factors for poor outcome in AES

Factor	Morbidity/ Mortality (n=17)	Normal (n=33)	p value
Posturing	5(29.4%)	1(3.0%)	.014
Abnormal spinomotor examination	8(47.1%)	3(9.1%)	.004
Abnormal EEG	6(35.3%)	4(12.1%)	0.013
Abnormal neuroimaging	13(76.5%)`	9(27.3%)	0.002

DISCUSSION

AES in children is a syndrome of various neurological illnesses with significant rate of morbidity and mortality. Mortality rate in our study was 8% and poor outcome of severe sequelae was observed in 12 % at discharge (6% discharged and 6% left against medical advice) and minimal disability in 14%. There is a wide variation (0 to 30%) in the mortality rate reported in other studies[3-4,11]. In our study, 26% of children survived with sequelae. Presence of posturing, abnormal signs on spinomotor examination, abnormal EEG findings and abnormal neuroimaging findings were individually associated with mortality or morbidity. Similar observation has been made in other studies[12-14].

In 31 (62%) children, a definitive diagnosis could be made and in 19 (38%) cases, we could not determine the etiology. This pattern and rate of difficulty in identification of etiology has been documented in other studies as well[4-6,7,15]. Possible reasons are AES meningitis.

There is a wide variation in the viral etiology of AES across various geographical locations. In our study, we had dengue encephalitis as a commonest cause. Though the nervous system manifestations in dengue are rare, it is being reported with increased frequency particularly in endemic areas[16]. In a large study in six district hospitals of Uttar Pradesh, West Bengal, and Assam over 4 years, nearly half the cases (49.2%) had an aetiology established and the three important causative organisms were JE (16%), scrub typhus (16%) and dengue (5%)[9]. Pathogenesis involved in central nervous system manifestations of dengue fever needs to be elucidated. We had only one case of Japanese B encephalitis. This decreasing trend of JE encephalitis is also the observation from other studies probably owing to the routine coverage with JE vaccine in endemic districts of the country[17].

We had 16% of cases with bacterial etiology and this finding reinforces the difficulty encountered in distinguishing bacterial and viral meningitis on clinical background of AES. 10% of cases turned out be due to Mycobacterium tuberculosis and this type of acute presentation has to be expected in a country like India, where tuberculosis is highly prevalent.

We had one case of scrub typhus encephalitis and this is an emerging problem in this part of country[18]. It is important to diagnose this, as early treatment can lead to complete recovery. Similarly, diagnosis of autoimmune encephalitis(AIE) could be established in one case. AIE and acute demyelinating encephalitis (ADEM) are increasingly reported in AES and they are important to diagnose as specific treatment modalities are available[19-21].

Of interest, we had AES like presentation of conditions like GBS, Rassmussen encephalitis, and Hepatitis A induced encephalopathy in one case each.

We could identify the etiology in majority of cases due to the availability of various investigational modalities but could not study all the known viral causes of encephalitis. That was a limitation of the study besides the relatively less number of affected children.

CONCLUSION

With inclusion of JE vaccine in immunization schedule, AES occurs commonly due to diseases that are endemic like dengue and tuberculosis and less due to JE. We should be vigilant for emerging diseases like scrub typhus as the cause of AES and also about AES like presentation of bacterial meningitis and auto immune diseases, all of which have specific treatment modalities. Increased access to diagnostic tests at referral hospitals will aid in making specific diagnosis, as AES is not an unitary disease of JE, but a syndrome. Periodic review of data of AES from sentinel centres will aid in possible paradigm shift in treatment and prevention including immunization and vector control measure.

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Informed consent: Informed consent is obtained from the caregivers of the children before the beginning of the study**.**

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