ORIGINAL RESEARCH PAPER

Pediatrics

KEY WORDS: Acute Encephalitis Syndrome (AES), JE confirm, AES unknown, *Glasgow Outcome Scale (GOS)*..

Etiology and prognostic factors of Children admitted with suspected Acute Encephalitis Syndrome in Tertiary level Hospital, Patna

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ABSTRACT

OBJECTIVES: To study the correlation between etiologies and outcome of suspected AES in the children of Patna,Bihar and to assess the prognosis of these children in relation to etiologies**.**

METHODS: Retrospective study among children suffering from encephalitis hospitalized at pediatrics ward of Nalanda Medical College Hospital, Patna. A total of 196 hospitalized suspected AES cases were enrolled from April 15 to April 17, Serum and cerebro spinal fluids were tested for biochemisty and cytology and by enzyme immunoassay for IgM antibodies was performed for measles virus, mumps virus, varicella zoster virus, herpes simplex virus , and Japanese encephalitis virus

RESULTS: 196 patients were enrolled in the study. 54 cases lebelled as AES unknown (29 death), only 7 cases were found to be JE positive (3 death), 123 case were found to be of non viral etiologies such as mningits TBM, malaria etc.(death 22 cases)..

CONCLUSIONS: Both Mortality and sequlae rate was highest in AES unknown followed by JE and lowest among non viral etiology, because untreatable causes have higher mortality

Introduction

Acute encephalitis syndrome (AES) is characterized by an acute onset of fever and clinical neurological manifestation that includes mental confusion, disorientation, delirium, or coma . Viruses have been mainly attributed to be the cause of AES in India although other sources such as bacteria, fungus, parasites, spirochetes, chemical, and toxins have been reported over the past few decades. The causative agent of AES varies with season and geographical location, and predominantly affects population below 15 years (1).

In recent times, that is, after 2012, AES cases in India have shifted towards the JE aetiology. till the end of November, 2,205 people were reported to be affected by JE, and the death toll due to JE rose up to 590 . JE was the major cause of these deaths,and virologists identified another causal agent in the form of 'toxin-mediated illness' and hypothesized the causal agent as a toxin prevalent in the litchi fruit . In these cases, encephalitis was not confirmed, rather encephalopathy with hypoglycaemia was observed.

While epidemics have a singular etiology, sporadic cases are more likely to be due to multiple etiologies, which require testing for multiple pathogens for effective surveillance. Despite advances made in virology in recent decades, the technology to detect these agents is expensive and often not available outside reference laboratories. This makes periodic hospital-based epidemiological investigations essential to determine the spectrum of agents that cause AES. We designed this retrospective study to answer specific research questions (a)what is the spectrum of etiological agents causing viral encephalitis in and around Patna and (c) what are the prognostic factors/ predictors of mortality in patients with AES,(c) what is the correlation between etiologies and outcome of AES among childrens of Patna.

Material And Methods

Children with AES upto 12 years of age who admitted in our pediatric ward of Nalanda Medical College & hospital (bihar , India) were included in this study during april 2015 to April 17. This is a tertiary level hospital which provides health care services to all districts in bihar. Most patients are referred to this apex level institute from periphery because of lack of intensive care facilities in the periphery.

For investigating AES cases, WHO Case definition (2) of was used which 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, come, 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 behaviour greater than that seen with usual febrile illness.

Case classification :

a) Laboratory-confirmed JE: A suspected case that has been laboratory-confirmed as JE.
b) Probable JE: A suspected case that occurs in close geographic and temporal relationship to laboratory-confirmed case of JE, in the context of an outbreak.
c) Acute encephalitis syndrome (due to agent other than JE): A suspected case in which diagnostic testing is performed and an etiological agent other than JE virus is identified.
d) Acute encephalitis syndrome (due to unknown agent) A suspected case in which no diagnostic testing is performed or in which testing was performed but no etiological agent was identified or in which the test results were indeterminate

Exclusion criteria- Such Patients were excluded if they: (a) had other severe disease, such as severe infection other than in the central nervous system, malignancy, brain infarction or cerebral hemorrhage, (b) a diagnosis of delirium or encephalopathy secondary to sepsis, toxins, or metabolic disorder.

All case sheets were retrospectively examined, patient fulfilling WHO case definition were selected and findings and data collected on a predesigned proforma. All data were analyse statistically. As per standard operating procedure, we were using following method for investigating cases of AES at our centre.

1) After getting written informed, consent 2 mL of blood and CSF samples were collected in sterile condition. The samples were then transferred under cold chain to Regional Medical Research Centre Laboratory, RMRI, Agamkuan for further analysis. Reports of CSF samples analyzed for physical, chemical, and cytological examination and other relevant investigations done at the time of admission were recorded from the bed head tickets of the patient.
2) JE virus specific IgM antibodies were detected by IgM antibody capture-enzyme-linked immunosorbent assay kits. the JEV-IgM positive samples were further tested for the presence of IgM antibody against other flaviviruses namely Dengue West Nile, and chandipura virus, enteroviuses etc by using IgM capture ELISA kit.

3) The outcome of the patients were recorded at the time of discharge. The outcome of patients was graded with a functional outcome score (Glasgow Outcome Scale, GOS),as follows:I death; II severe sequelae greatly impairing function and incompatible with independent living; IIImoderate sequelae mildly affecting function (including seizures), but compatible with independent living; IV minor sequelae including altered personality or clinical signs not affecting functions; V full recovery and normal neurologic examination findings (3)..

Observation-

196 patients were enrolled in the study. only 7 case (%) were found to be JE positive(3 death), 54 cases lebelled as AES unknown (29 death), 123 case were found to be of non viral etiologies such as mningits ,TBM,malaria etc.(death 22 cases)

Study flow chart

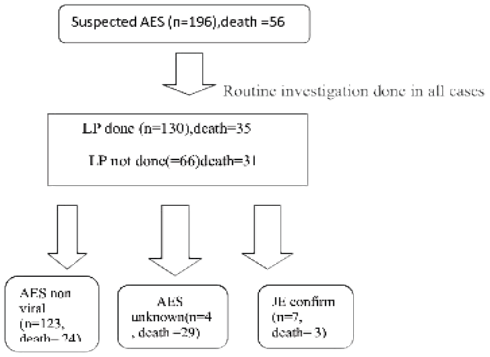

Table-1 Etiology and outcome data

Cases	Suspected AES	AES of non-viral aetiology	JE confirm	AES unknown	Non JE	Probable JE
Number	196	123	7	54	Nil	Nil
Death	56 (28.52%)	24 (19.51%)	3(42.85%)	29(43.93%)	Nil	Nil
Recovered completely (GOS V)	104(55.10%)	53 (43.08%)	1(1428%)	11(16.66%)	Nil	Nil
Recovered with neurological sequel (GOS II –IV)	28(14.28%)	36 (29.26%)	3(42.85%)	12(18.18%)	Nil	Nil
LAMA	8 (4.08%)	10 (8.13%)	I (14.28%)	3 (4.54%)	Nil	Nil

Table-3 clinical parameter and death data

Features	Number	Death	Percentage (%)
Fever	196	56	(28.57%)
Altered sensorium	146	43	(29.45%)
Headache	128	52	(40.62%)
Irritable	93	20	(21.50%)
Abnormal behaviour	82	16	(19.51%)
Diarrhoea	53	15	(28.30%)
Seizure	94	28	(29.78%)
Glasgow coma scale (GCS) □ 8	77	31	(40.25%)
Signs of meningeal irritation	92	23	(25.00%)
Limb weakness	64	29	(45.31%)
Shock on admission	66	32	(46.96%)
Aspiration syndrome	51	22	(43.13%)
Early presentation(<5 days illness)	65	14	(21.53%)
Hospital stay >7days	84	18	(33.33%)
Need for mechanical ventilationYes	5 4	15	(46.29%)
Recurrent seizures Yes	35	11	(31.42%)
Neuroimaging changes	28	5	(17.85%)
Hypoglycemia	17	2	(11.76%)

Discussion

This study demonstrates that patients with AES of suspected viral aetiology, either where JE was confirmed or where viral aetiology remained unknown, were significantly more likely to have a bad outcome compared to AES patients with bacterial or malaria infection.(Table-1)

The lower frequency of bad outcome among the AES patients with bacterial or malaria infection is likely to reflect the availability and effective use of antibiotics and anti-malaria treatment to reduce morbidity among these patients.

AES patients without LP results exhibited a significantly higher rate(46.96%vs 26.92%) of death. The finding is likely to reflect lumbar punctures being undertaken less frequently on children who were critically ill.(Flow chart)

This study has identified that the number of days of fever (reflecting number of days of illness) the patient experienced prior to hospital admission is a prognostic indicator of bad outcome in both patients with AES of unknown viral aetiology and JE. Shorter duration of illness (or fever) prior to admission has previously been associated with good outcome among children for a range of diseases(4) . What is striking about our finding is that there is no specific treatment for JE or AES of suspected viral aetiology, yet attending hospital earlier in the illness course appears to be of benefit. The findings would suggest that hospital admission and the supportive management received there improves outcome.Another finding is that longer duration of hospitalisation carries poor prognosis.(Table-3)

Patients with impaired consciousness are often unable to drink themselves. Consequently, dehydration and metabolic acidosis may complicate AES (5). Dehydration and acidosis would fit the significantly lower body weight and higher respiratory rate observed among JE compared to Non-JE patients.

As shown previously, a low Glasgow coma scale (GCS) and/or a focal neurological deficit at hospital admission were independent clinical markers of bad outcome among children with AES (6). JE patients frequently exhibit raised intra-cranial pressure, brain herniation syndromes (6) and focal brain lesions on neuro-imaging studies (7), explaining the preponderance of focal neurolgical deficit and residual disease s in this group.Hypoglycemia has got lesser mortality(11.76%)

Strenghth of this study is that this is a comprehensive clinical and virologic descripton of children with suspected AES, in a setting with high quality hospital-based surveillance. We observed that this type of hospital based surveillance systems can help track changes in encephalitis patterns. While viral diagnostics are resource intensive, we should focus on standard protocols for identification of AES and basic CSF based diagnostics into routine clinical care, as has happened after completion of study at this hospital. Periodic diagnostic testing can provide valuable etiologic and epidemiologic information.

Our study also has certain limitations,(a) the definition of AES is clinical and subject to clinical interpretation. This leads to result in over-inclusion of non-encephalitic cases as AES.(b), the risk of disease and hazard of mortality or disability is likely to be etiology-specific, but in most of the AES cases, did not have a specific etiology identified. However this limitation is true of many similar studies. (c) all AES cases included in this study were sampled from a single hospital, and it is likely that we missed those children who never sought medical care for their symptoms or sought care at another facility. Although patient in lower socio-economic status are likely to prefer state-funded facility where the study was conducted. Since AES is more likely to affect lower socio-economic population, we expect sampling bias to only moderately underestimate the overall incidence. Overall hospital-based nature of the study can lead to underestimation of the true incidence of AES since milder, non-hospitalized cases are not captured.(d) we used only commercially available diagnostics to look for common

organisms which cause AES. We did not test for Rabies, Simian retroviruses, and other fungal or parasitic organisms. (e) we are not performing or post-mortem examination in cases with mortality. It is likely that many AES cases of unknown etiology are due to less common or as yet unknown agents. Future studies may help in understanding etiology of some of these cases.

Conclusion-

Aetiolology of majority of AES remain obscure. JE is still a major cause of AES in children in this part of India and no other virus was detected at all. The case fatality rate was recorded high as 42.85% due to JE and 43.93% AES unknown cases in children admitted with AES. AES cases due to non viral etiology have less mortality. Presence of shok on admission, prolonged hospitalisation, ,presence of limb weakness, need for ventilation were found associated to bad outcome. Further research is needed to understand the factors that underlie bad outcome in AES and JE, including a more systematic investigation for cause and of the influence of supportive measures.

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Conflict of Interests The authors declare that they have no conflict of interests.:

Authors' contributions- AR,AS designed the study. AR acquired and undertook initial analysis of the data. AR interpreted the data. AR wrote the manuscript. All authors read and approved the final manuscript.

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