Clinico-epidemiological presentation of acute encephalitis syndrome in patients visiting a tertiary hospital in Kathmandu, Nepal: A descriptive cross-sectional study

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ABSTRACT

Introduction: Acute encephalitis syndrome is diagnosed when a person of any age, and at any time of the year, presents with the acute onset of fever and a change in mental status and/or new onset of seizures. It has an ill-defined clinico-epidemiological presentation in Nepal, making it a challenging medical condition. The objective of this study was to study the clinical profile of acute encephalitis syndrome. **Methods:** All consecutive admissions at Tribhuvan University Teaching Hospital between April 2017 and December 2018 were screened for acute encephalitis syndrome. The diagnosis was confirmed by history, examination, laboratory findings, brain imaging, and electroencephalography. All patients who met the inclusion criteria were enrolled. For data entry and analysis, statistical package for the social sciences software version 16.0 was used. Descriptive statistics as frequencies and mean ± standard deviations were computed. **Results:** The mean age of the study population was 49.56±22.28 years with male predominance 42(58.3%). Among the diagnosed etiologies, 1.38% had Japanese encephalitis, 4.12% had herpes encephalitis, and 4.12% had autoimmune encephalitis. Out of the 72 patients, 52 patients (72.22%) had Glasgow coma scale >12, 15 patients (20.83%) had 8 to 12, and five patients (6.94%) had coma (Glasgow coma scale <8). Among the clinical findings, altered mental status (91.66%) was the most commonly noticed manifestation followed by fever. **Conclusions:** Most patients had altered sensorium with less severe brain injury based on the Glasgow coma scale score during the presentation. Its low diagnostic yield, however, often leads to an increase in unknown etiologies. The syndrome was more prevalent in hilly regions.

Keywords: Acute encephalitis syndrome, altered sensorium, Japanese encephalitis.

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INTRODUCTION

Acute encephalitis syndrome (AES) has been a major health concern around the globe because the disease is associated with high morbidity and mortality rates. AES (simply known as brain fever) is a constellation of symptoms and signs, characterized by acute onset of fever and a change in mental status, such as disorientation, confusion, coma, or inability to speak, as well as onset of new seizures (except febrile seizures) due to inflammation of brain.[1] Because AES caused by different etiological agents show similar clinical characteristics, this broad syndromic definition is primarily used for disease surveillance. AES can occur as a sporadic or explosive outbreak. Many neurotropic viruses and non-viral etiologies can cause AES, making diagnosis challenging.[2] There have been outbreaks of Japanese encephalitis virus (JEV) in Nepal.[3] According to current estimates, 12.5 million people in Nepal are at high risk for JE. Over the past several decades, the JE-endemic region has spread from 24 districts in the southern plains to districts in the

neighboring hills and mountains in the north, including the densely populated Kathmandu Valley.[4] No specific research has been conducted on the incidence of AES. Nevertheless, there were studies from various countries that examined the incidence of encephalitis in different settings. During an epidemic in Nepal in 1997, an incidence rate of 145 to 185 was recorded.[5] In Nepal, cases of acute encephalitis syndrome (5.23/100,000) are estimated to be more than 12 times higher than in India (0.42/100,000).[6] In our scenario, knowledge of this disease is limited, limitations in investigations and diagnostics, and challenges in the management of critically ill patients.[3] Therefore, this study was conducted to assess the clinical spectrum of AES in patients visiting the Institute of Medicine, Nepal.

METHODS

All the patients aged 16 years and older admitted to the inpatient wards and critical care units of the Department of Neurology, Institute of Medicine with acute encephalitis syndrome between April 2017 and December 2018 were included. The cases of encephalitis were limited to those patients who met the following criteria: patients with fever or history of fever with change in mental status (including confusion, disorientation, coma, or inability to talk) and or new onset of seizures at any time of year, all subjects with a diagnosis of encephalitis. Cases with a diagnosis of delirium or encephalopathy secondary to sepsis, toxins, metabolic causes (hypoglycemia, electrolyte disturbances, Wernicke's encephalopathy), patients having cerebrovascular disease followed by fever, traumatic brain injury, malignant hypertension, neuroleptic malignant syndrome, epilepsy, systemic organ dysfunction, systemic infection that spreads to brain (e.g. Malaria), tuberculer meningoencephalitis, bacterial meningoencephalitis, patients diagnosed with Acute disseminated encephalomyelitis (ADEM) were excluded.

A detailed history was obtained and general and systemic examination was performed meticulously. Then, all required investigations: complete blood count (CBC), erythrocyte sedimentation rate, renal function test (serum urea, serum creatinine, Na^+, K^+), random blood sugar, serology (ELISA for HIV I and II, HBsAg IgG, Anti-HCV Antibody), urine routine examination, cerebrospinal fluid (CSF) analysis-CSF pressure, total leukocyte count, differential leukocyte count, sugar, protein, gram stain and C/S, HSV I & II polymerase chain reaction (PCR), varicella zoster PCR, Anti-JE IgM and tropical fever panel (Dengue virus, Rickettsia species, Salmonella species, West Nile virus, Plasmodium species, Chikungunya virus, and Leptospira species) and anti–NMDA receptor antibody, acid-fast bacilli and blood C/S were sent. Magnetic Resonance Analysis (MRI)-Brain, electroencephalography, and chest x-ray were done and medical management was started. Once the culture and sensitivity report arrived, anti-microbial was changed accordingly. Autoimmune encephalitis was confirmed by the presence of anti-NMDA-R antibodies. Blood pressure (BP), pulse rate (PR), Glasgow coma scale (GCS), respiratory rate, temperature, and oxygen saturation (SpO2) were monitored regularly and strict input and output chart was maintained. Ethical clearance was obtained from the Institutional review board, institute of Medicine, Tribhuvan University [Ref: 80 (6-11-E)^2/074/075]. Written informed consent was obtained from the patients, or their legal surrogates for children below 18 years) before enrolment. Statistical package for social sciences (SPSS) software version 16.0 was used for data entry and analysis. Descriptive statistics were used for analysis. Descriptive statistics were expressed as frequencies, mean ± SD and range.

RESULTS

After the exclusion of other causes of altered sensorium, 72 patients who met the inclusion criteria were included in the study. The mean age of the study population was 49.56±22.28 years ranging from 16 years to 94 years. Most patients presenting with acute encephalitis syndrome were 16- 30 years and 46-60 years of age group. There was notable male preponderance 42(58.33%). No cases were reported from the mountain region during the course of the present study (Table 1).

Table 1: Clinico-epidemiological patterns among the study participants (n=72)

Variables	n(%)
Age group (years)	
16-30	18(25%)
31-45	13(18.05%)
46-60	18(25%)
61-75	14(19.44%)
76-90	7(9.72%)
>90	2(2.77%)
Geographic location	
Hills	47(65.27%)
Terai	25(34.72%)
Clinical features	
Altered Sensorium	66(91.66%)
Fever	52(72.22%)
Headache	52(72.22%)
Focal Neurological Deficit	26(36.11%)
Seizure	25(34.72%)
Loss of Consciousness	18(25%)
Meningeal Signs	13(18.05%)

The most common comorbidity was hypertension which was present in 21(29.16%) of the study population,

followed by diabetes mellitus in 15(20.83%), chronic kidney disease 7(9.72%), coronary artery disease 7(9.72%) and chronic liver disease in 7(9.72%), and HIV in 5(6.94%) cases.

Most of the patients 52(72.22%) had GCS>12 (Table 2).

Table 2: Glasgow coma scale group among the study population (n=72)

GCS	Number (n)	Percentage (%)
<8	5	6.94
8-12	15	20.83
>12	52	72.22

Among the study population, 16 patients (22.22%) had BP more than 130/80 mmHg and 56 patients (77.77%) had BP less than 130/80 mmHg. Regarding pulse rate, 64 patients (88.88%) had PR of fewer than 100 beats/min and eight patients (11.11%) had PR of more than 100 beats/min.

Most of the cases 65(90.27%) had unknown etiology. (Table 3)

Table 3: Etiological characteristics among the study population (n=72)

Characteristics	Variables	Value
Etiology	JE	1(1.38%)
	HSV	3(4.16%)
	Autoimmune	3(4.16%)
	Unknown	65(90.27%)

Table 4: Summary of CSF analysis characteristics among the study population (n=72)

Characteristic	Variable	Value n (%) or mean ±SD (Range)
Total Count ($\times 10^3/mm^3$)		88.51±137.06 (5 to 800)
Differential Count	Polymorphs ($\times 10^3/mm^3$)	34.20±80.91 (1 to 480)
	Monomorphs	54.23± 98.84 (1 to 760)
	Polymorph predominant	12 (16.66%)
	Monomorph predominant	60 (83.33%)
CSF Biochemistry	Glucose	3.33 ± 1.84 (1.00 to 8.00)
	Normal	34 (47.22%)
	Low	38 (52.77%)
	Protein	55.74± 20.36 (17.00 to 110.00)
	Normal	15(20.83%)
	Low	1(1.38%)
	High	56(77.77%)
CSF Serology	No growth	68(94.44%)
	HSV PCR positive	3(4.16%)
	Anti JE Antibody positive	1(1.38%)

More than half of the patients had low CSF glucose and high CSF protein. Only four cases had a viral cause of the disease (Table 4).

DISCUSSION

As the primary presenting feature, altered sensorium was most frequently encountered in our study followed by fever and headache, which contrasts with Dongol et al. [7], who reported fever as the most common finding among 100% of their study participants. In their study, altered sensorium was found in only 18.75% of participants. Tripathy et al.[1] also found that 100% of their participants had a fever. Their study, however, involved only pediatric participants under 15 years old. The observation of our study was similar to the study conducted by Jameel et al.[8] where 80.48% of patients had mental status changes followed by fever (79.26%). A study conducted by Rayamajhi et al.[9] had, however, all of their 36 patients presenting with fever and headache. The seizure was found in 25(34.72%) participants in our study. The study conducted by Jameel et al.[8] reported seizures in 97(59.14%) patients whereas 44.64% of pediatric patients had seizures in a study by Dongol et al.[7] Tripathi et al.[1] found that 53.23% of pediatric participants had seizure symptoms. There was a 1.12 odds ratio associated with seizure-related mortality, but it was not statistically significant. The risk of mortality was significantly increased when intracranial pressure was raised, assisted ventilation was required, and hypotension was present.

Additionally, when we evaluated the mean age of study participants, the results showed significant differences compared to the previous study conducted between March 2009 and March 2010 in the same setting to study predictors of outcome in acute encephalitis. The participants in their study were younger with a mean age of 34.83±14.34.[9] The mean age was comparable to a study by Rayamajhi et al.[9] conducted in the same setting who reported mean age of 43±18 years.

Our study showed male preponderance which is in line with previous studies.[7-9] A possible explanation for this variation could be increased outside activities, exposure, or stress. In addition, women may feel stigmatized or seek health services less often as a result of low health-seeking behaviors, resulting in an inflated presentation rate of males.

The present study is focused on cases from Kathmandu, the capital city that drains cases from all over Nepal. In our study, no cases were reported from the mountain region, which may be attributed to the mountain region being sparsely populated or due to exodus for employment and education. Highest reported cases were from the hilly region followed by the terai region, which contested the findings of Thapa et al. where a larger proportion was

from the terai region. The geographical variation in the study might be due to differences in the place of study, the differences in the catchment area of the hospital, and referral bias.[10]

Although encephalitis covers a wide variety of known pathologies, diagnostic tests for AES usually produce very low diagnostic yields. The etiology of more than 90% of cases remains unknown in the current study. In previous studies, at least a third of all cases remained undiagnosed. Among the total, 1571 encephalitis patients evaluated over a seven-year period, only 15% had an infectious etiology, as seen in the California Encephalitis Project.[11] The most common etiology in the current study was herpes encephalitis (n=3) and autoimmune encephalitis confirmed by the presence of NMDA antibody (n=3). Only one case of JE was observed. Earlier studies reported enteroviruses as one of the predominant causative agents of encephalitis.[2,11,12] A north Indian hospital-based surveillance study reported that 20(13%) of all 151 AES cases had evidence of an enteroviral infection.[13] Normally, enteroviruses only reside in the CSF for a short time before translocating to the brain parenchyma. Consequently, some patients with encephalitis of unknown cause may have had enteroviral encephalitis, which is only detectable by tissue PCR.[2]

A resounding success has been achieved in the prevention and control of JE in Nepal, especially after it incorporated CD-JEV into its Expanded Program on Immunization (EPI) for children in high-risk districts. There may be herd immunity against JEV due to the widespread use of the JE vaccine. In a six-year surveillance period from 2004 to 2009, surveillance data showed that, after the campaigns, JE incidence was 72% lower than what might have occurred otherwise.[4] AES patients have compromised respiratory drives and require assisted ventilation if they have brain-stem encephalitis or cerebral herniation. The high GCS at admission is protective as it implies less neurologic damage. The majority of our study participants had GCS>12(72.22%). There was an elevated white blood cell count with predominantly lymphocytic pleocytosis (83.33%). Low glucose (52.77%) and raised protein level (77.77%) was noted. Possible contributors to decreased CSF glucose could be increased metabolism in the brain.

Our study has several limitations. Considering that all of the AES cases included in this study came from one hospital, it is likely that we missed those individuals who never sought medical care or sought care in another institute. Since AES is more likely to affect lower socio-economic populations, we expect sampling bias to only moderately underestimate the overall incidence. The nature of the study being hospital-based can lead to misrepresentation of AES since milder, non-hospitalized cases were not captured. Future efforts to estimate the community burden of AES are needed. A long-term follow-up of survivors, as well as neuropsychological evaluation, beyond the hospital stay, was not possible due to the design of the study. Future study recommendations could include participants from multiple centers throughout the country and analyze their clinical spectrum.

CONCLUSIONS

Clinically, altered sensorium was the most common clinical presentation, followed by fever, vomiting, and headaches. As observed in our study, AES often results in an increased number of cases with unknown etiology due to its poor diagnostic yield. We, thus, conclude that diagnostics for acute encephalitis syndrome require a significant amount of resources, however, standard protocols can be incorporated to identify AES.

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