Correlation between clinical-laboratory profile and outcome of AES cases in children: A hospital-based study

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ABSTRACT

Objective: This study aims to determine the correlation between clinical as well as laboratory profile changes with the outcome of acute encephalitis syndrome (AES) cases. Materials and Methods: This prospective observational study was conducted in the Department of Pediatrics at Jorhat Medical College and Hospital, Assam over a period of 1 year where 49 diagnosed cases of AES in children aged between 1 month and 12 years were enrolled. Results: The study found that fever (100%) and altered sensorium (100%) were the most common clinical presentations in AES cases, followed by seizure (63%), headache (34.7%), vomiting (26.5%), diarrhea (22.4%), etc. Japanese encephalitis (JE) was the most common cause of AES (28.6%), followed by herpes simplex virus (4.1%), pyogenic meningitis (4.1%), and tubercular meningitis (2%), etc. However, the majority of cases (61.2%) were found to have an unknown etiology. Among the 49 cases, 27 (55.1%) recovered without neurological sequelae, 8 (16.8%) had neurological sequelae, and 14 (28.6%) died during the course of treatment. The most common neurological sequelae observed were motor deficit (37.5%), behavioral disorders, aphasia (25% each), and cranial nerve palsy. Glasgow coma scale (GCS) at the time of admission and during the time of hospital stay was found to have a significant (p<0.05) correlation with outcome in AES patients. Conclusion: The study concludes that AES cases commonly present with fever, altered sensorium, seizure, headache, vomiting, and signs of meningeal irritation. JE remains a major known cause of AES in children in this region of India. GCS at the time of admission and during the time of hospital stay were found to have a significant correlation with outcome. The neurological sequelae highlight the need for global attention to combat them save the lives of children.

Key words: Acute encephalitis syndrome, Glasgow coma scale, Meningitis

Acute encephalitis syndrome (AES) is a commonly encountered problem in pediatric clinical practice. It poses challenges to physicians owing to acute presentation, often rapid neurologic deterioration, and a high fatality rate. AES is defined as in 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). The cause of AES varies based on season and geographical location, with viruses being the most commonly attributed cause in India. However, other microbes and toxins have also been reported as causative agents in AES [1,2].

Children with AES often require admission to intensive care units and need specialized care. However, there is no specific treatment for AES, and management is primarily supportive [3]. This study aims to determine the correlation between the clinical-laboratory profile and outcomes of AES in children in a hospital setting. The study was conducted in the Pediatrics Department of Jorhat Medical College and Hospital (JMCH) in Assam over 1 year, and 49 diagnosed cases of AES were included in the study.

MATERIALS AND METHODS

This hospital-based and observational study was conducted at JMCH, a tertiary care facility that serves as a surveillance center for AES over a period of 1 year from June 1, 2020, to May 31, 2021. All children admitted to the Pediatrics Department of
JMCH during the study period and diagnosed with AES, who met the inclusion criteria, were included in the study.

**Inclusion criteria**

The following criteria were included in the study:

- Children diagnosed with AES according to the World Health Organization case definition
- Children aged between 1 month and 12 years whose parents provided an informed consent.

**Exclusion criteria**

The following criteria were included in the study:

- Children with a history of simple febrile seizures
- Patients with pre-existing neurological deficits before the onset of AES
- Neonates (aged from birth to 28 days).

**Methods**

This observational study was conducted at the Pediatrics Department of JMCH over a period of 1 year after getting approval from the Institutional Ethical Committee. Each patient was studied in a systematic manner using a pre-designed structural pro forma after written informed consent was obtained from their parents or guardians. Clinical variables such as heart rate, respiratory rate and patterns, blood pressure, temperature, sensorium using the modified Glasgow coma scale (GCS), pupillary response to light, posture, motor pattern (assessed subjectively by assessing passive tone), seizures (if any), type of seizure, and involuntary movement were recorded. After clinical examination, 2 mL of blood and 1 mL of cerebrospinal fluid (CSF) were collected and sent to the central clinical laboratory of JMCH, and relevant laboratory investigations such as immunoglobulin M enzyme-linked immunosorbent assay for Japanese encephalitis (JE) provided by the national institute of virology, Cartridge-based CBNAAT for tubercular meningitis, etc. were conducted. Rapid diagnostic tests and peripheral blood smears for malaria parasites were performed depending on the clinical presentation. The etiology of AES was classified into JE, bacterial meningitis, tubercular meningitis, cerebral malaria, and AES of unknown etiology. The outcome was recorded as recovery without neurological sequelae at the time of discharge, recovery with neurological sequelae at the time of discharge, or death.

**Data analysis**

Descriptive statistical methods were used to present the demographic characteristics. Data were analyzed by the use of statistical software (SPSS version 20, IBM). The Chi-square test and Fisher’s exact test were performed to test for differences in proportions of categorical variables between two or more groups. Student’s t-test was performed to compare the mean between the two groups. The level of p<0.05 is considered significant.

**RESULTS**

**Etiological profile**

JE was the most common cause of AES, accounting for 14 cases (28.6%), followed by herpes simplex virus (HSV) in 2 cases (4.1%), pyogenic meningitis in 2 cases (4.1%), and tubercular meningitis in 1 case (2%). The majority of cases, 30 (61.2%), had an unknown etiology.

**Clinical profile**

Fever and altered sensorium were present in all 49 cases (100%). Seizures were reported in 31 cases (63%), headaches in 17 cases (34.7%), vomiting in 13 cases (26.5%), and diarrhea in 11 cases (22.4%). Other symptoms reported included excessive crying and irritability, which were observed in 11 cases (22.4%) (Table 1).

**Outcome of AES at the time of discharge**

Among the 49 AES cases, the majority of cases 27 (55.1%) recovered without neurological sequelae, 8 (16.8%) cases suffered from neurological sequelae, and 14 (28.6%) cases expired during treatment. The most common neurological sequelae were motor deficit (37.5%), followed by behavioral disorders 2 (25%), aphasia 2 (25%), and cranial nerve palsy 1 (25%).

**Correlation of GCS at admission affecting the outcome**

Out of 49 AES cases, 12 cases had GCS between 3 and 8, out of that 8 (66.7%) cases expired, 3 (25%) cases recovered with neurological sequelae, and only 1 (8.3%) case recovered without neurological sequelae. Fourteen cases had GCS between 9 and 12, out of that 6 (42.9%) cases expired, 4 (28.6%) cases recovered with neurological sequelae, and 4 (28.6%) cases recovered without neurological sequelae. Twenty-three cases had GCS between 13 and 15, out of that 22 (95.7%) cases recovered without neurological sequelae, and 1 (4.3%) case recovered with neurological sequelae (p=0.001, <0.05).

**Correlation of duration of hospital stay and outcome**

The patients who stayed in the hospital for the duration between 0 and 7 days either recovered without neurological sequelae 12 (50%) or expired 12 (50%) and patients who stayed in the hospital for a duration >15 days had neurological sequelae 5 (83.33%) (p=0.001, <0.05) (Table 2).
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Laboratory profile

**Serum sodium level**

Out of 49 AES cases, 13 cases had serum sodium <135 meq/l, out of that 7 (53.8%) cases recovered without neurological sequelae and 6 (46.2%) cases expired during treatment. Thirty-three cases had serum sodium between 135 and 145 meq/l, out of that 19 (57.6%) cases recovered without neurological sequelae, 8 (24.2%) cases recovered with neurological sequelae, and 6 (18.2%) cases expired during treatment. Three cases had serum sodium of more than 145 meq/l, out of that 2 (66.7%) cases expired during treatment and 1 (33.3%) case recovered without neurological sequelae (p=0.079, >0.05).

**Serum potassium level**

Out of 49 AES cases, 42 cases had Serum Potassium between 2.5 and 5.5 mmol/l, out of that 22 (52.4%) cases recovered without neurological sequelae, 7 (16.7%) cases recovered with neurological sequelae, and 13 (31%) cases expired during treatment. Seven cases had serum potassium between >5.5 mmol/l, out of that 5 (71.4%) cases recovered without neurological sequelae, 1 (14.3%) case recovered with neurological sequelae and 1 (14.3%) case expired during treatment (p=0.607, >0.05).

**Total leukocyte count**

Out of 49 AES cases, 28 cases had blood total leucocyte count (TLC) of more than 11000 cells/mm³, out of that, 14 (50%) cases recovered without neurological sequelae, 5 (17.9%) cases recovered with neurological sequelae, and 9 (32.1%) cases expired during treatment. Twenty-one cases had Blood TLC between 4000 and 11000 cells/mm³, out of that, 13 (60%) cases recovered without neurological sequelae, 3 (15%) cases recovered with neurological sequelae, and 5 (25%) cases expired during treatment (p=0.788, >0.05).

**CSF cell count**

Out of 49 AES cases, 26 cases had CSF cell count between 0 and 5 cells/mm³, out of that 16 (61.5%) cases recovered without neurological sequelae, 4 (15.4%) cases recovered with neurological sequelae, 6 (23%) cases expired during treatment. 23 cases had CSF cell count of more than 5 cells/mm³, out of that 11 (47.8%) cases recovered without neurological sequelae, 4 (17.4%) cases recovered with neurological sequelae, and 8 (34.8%) cases expired during treatment (p=0.597, >0.05).

**CSF protein**

Out of 49 AES cases, three cases had CSF protein ≤40 mg/dl, out of that 1 (33%) cases recovered without neurological sequelae, and 2 (66.7%) cases expired during treatment. Forty-six cases had CSF protein of more than 40 mg/dl, out of that, 26 (56.5%) cases recovered without neurological sequelae, 8 (17.4%) cases recovered with neurological sequelae, and 12 (26.1%) cases expired during treatment (p=0.298, >0.05).

**DISCUSSION**

Our study reveals that viral encephalitis, particularly JE (28.6%), is the leading identified cause of AES, followed by HSV (4.1%), pyogenic meningitis (4.1%), and tubercular meningitis (2%). However, in a substantial proportion of cases (61.2%), the cause remained unidentified. These findings are in accordance with previous research, such as the study by Basu and Kalamuddin, which similarly reported viral encephalitis as the primary cause of AES, followed by bacterial and tubercular meningitis [3].

The clinical profile of AES in our study reflects consistent patterns, with fever and altered sensorium being universal symptoms (100%). Seizures (63.3%), headache (34.7%), vomiting (26.5%), and diarrhea (22.4%) were also frequently observed. These findings echo earlier studies by Khinchi et al.; Basu and Kalamuddin, reinforcing fever and altered sensorium as predominant symptoms in pediatric AES cases [3,4].

Our observations regarding serum sodium levels align with studies by Sambasivam et al.; Prakash Sahay and Irfan, emphasizing the association of hyponatremia with higher morbidity and mortality [5,6]. However, our study did not find a significant correlation between serum sodium levels and overall outcome, contrasting with adult AES studies conducted by
Barman et al., suggesting the need for further investigation into age-specific factors [7].

In present study, majority of patients who recovered without neurological sequelae (14, 50%) had TLC >11000 cells/mm$^3$. Maximum number of patients who recovered with neurological sequelae (5, 17.9%) had TLC >11000 cells/mm$^3$. Maximum number of patients who expired (9, 32%) had TLC >11000 cells/mm$^3$. Similar observations made by earlier study Sambasivam et al. and Prakash Sahay and Irfan and found no significant association between TLC and outcome of AES patients [5,6].

In our study, mean value for CSF cell count was 17±30 Cells/mm$^3$ and a mean value for CSF protein was 51±23 mg/dl. There was no significant correlation between CSF cell count and CSF Protein with outcome in AES patients as the p=0.597 and (0.298), respectively. Kakoti et al. also found mean value for CSF cell count and protein 42.63±82.11 Cells/mm$^3$ and 45.6±12.4 mg/dl respectively with no significant association between high CSF cell count and protein [8].

In our study, majority of cases, 27 (55.1%) recovered without neurological sequelae, 8 (16.8%) recovered with neurological sequelae, and 14 (28.6%) expired in hospital during treatment which is comparable to the study done by Basu and Kalamuddin where they found 88 (63.8%), 15 (10.9%), 34 (25.3%) and 82 (57.74%), 33 (23.23%), 27 (19.01%), respectively, recovered cases without neurological sequelae, with neurological sequelae and expired cases [3]. However, De et al. showed dissimilarity in neurological sequelae (6 [25%], 11 [45.83%], 7 [29.16%]) probably due to geographical variation and selection criteria [9].

Our study showed motor deficit (3, 37.5%) as the most common sequelae followed by behavioral disorders (2, 25%), aphasia (2, 25%), and cranial nerve palsy (1, 25%). Basu and Kalamuddin found extrapyramidal (21, 63%) lesion as the most common form of neurological sequelae followed by aphasia (17, 51.51%), behavioral disorder (7, 21.21%) and motor deficit (2, 6.06%) which is contrary to our study. Khound and Dowerah had the observation aphasia (41%) as the most common neurological sequelae followed by behavioral abnormality (24%), motor deficit (20%), cranial nerve palsy (9%), and extrapyramidal abnormal movements (4%) [3,10].

Our study observed significant correlation between GCS and outcome in AES patients (p=0.001, <0.05). Maximum number of patients who expired 8 (66.7%) had GCS between 3 and 8, and those who recovered with neurological sequelae had GCS in the lower side between 3 and 8 (25%) or 9–12 (28.6%). Thus lower the GCS score, more the adverse outcome (death or sequelae). De et al. (2015) and Basu and Kalamuddin also found similar

### Table 2: Correlation of different variables affecting the outcome of AES cases (n=49)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Recovered without neurological sequelae n (%)</th>
<th>Recovered with neurological sequelae n (%)</th>
<th>Death n (%)</th>
<th>Significance (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–8</td>
<td>1 (8.3)</td>
<td>3 (25)</td>
<td>8 (66.7)</td>
<td>S (0.001)</td>
</tr>
<tr>
<td>9–12</td>
<td>4 (28.6)</td>
<td>4 (28.6)</td>
<td>6 (42.9)</td>
<td></td>
</tr>
<tr>
<td>13–15</td>
<td>22 (95.7)</td>
<td>1 (4.3)</td>
<td>0 (0.00)</td>
<td></td>
</tr>
<tr>
<td>Duration of hospital stay</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–7 days</td>
<td>12 (50)</td>
<td>0 (0)</td>
<td>12 (50)</td>
<td>S (0.001)</td>
</tr>
<tr>
<td>8–15 days</td>
<td>13 (50)</td>
<td>3 (37.5)</td>
<td>2 (14.3)</td>
<td></td>
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<tr>
<td>&gt;15 days</td>
<td>1 (16)</td>
<td>5 (83.3)</td>
<td>0 (0)</td>
<td></td>
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<tr>
<td>Serum sodium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;135 meq/l</td>
<td>7 (53.8)</td>
<td>0 (0.00)</td>
<td>6 (46.2)</td>
<td>NS (0.079)</td>
</tr>
<tr>
<td>135–145 meq/l</td>
<td>19 (57.6)</td>
<td>8 (24.2)</td>
<td>6 (18.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;145 meq/l</td>
<td>1 (33.3)</td>
<td>0 (0.0)</td>
<td>2 (67.7)</td>
<td></td>
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<tr>
<td>Serum potassium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5–5.5 mmol/l</td>
<td>22 (52.4)</td>
<td>7 (16.7)</td>
<td>13 (31)</td>
<td>NS (0.607)</td>
</tr>
<tr>
<td>&gt;5.5 mmol/l</td>
<td>5 (71.4)</td>
<td>1 (14.3)</td>
<td>1 (14.3)</td>
<td></td>
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<tr>
<td>CSF(cells/mm$^3$)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>0–5</td>
<td>16 (61.5)</td>
<td>4 (15.4)</td>
<td>6 (23)</td>
<td>NS (0.597)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>11 (47.8)</td>
<td>4 (17.4)</td>
<td>8 (34.8)</td>
<td></td>
</tr>
<tr>
<td>TLC (cells/mm$^3$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;4000</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>NS (0.788)</td>
</tr>
<tr>
<td>4000–11000</td>
<td>13 (60)</td>
<td>3 (15)</td>
<td>5 (25)</td>
<td></td>
</tr>
<tr>
<td>&gt;11000</td>
<td>14 (50)</td>
<td>5 (17.9)</td>
<td>9 (32.1)</td>
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<tr>
<td>CSF protein</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>≤40 mg/dl</td>
<td>1 (33.3)</td>
<td>0 (0.0)</td>
<td>2 (66.7)</td>
<td>NS (0.298)</td>
</tr>
<tr>
<td>&gt;40 mg/dl</td>
<td>26 (56.5)</td>
<td>8 (17.4)</td>
<td>12 (26.1)</td>
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</tbody>
</table>

AES: Acute encephalitis syndrome, TLC: Total leucocyte count, CSF: Cerebrospinal fluid
observations with a significant correlation (p<0.05) between the GCS score and outcome of AES patients [3,9].

In our study, we found a significant correlation between the duration of hospital stay and outcome in AES patients (p=0.001, <0.05). Patients who stayed in the hospital for the duration between 0 and 7 days either recovered without neurological sequelae 12 (50%) or expired 12 (50%) and those patients who stayed in the hospital for a duration >15 days were having neurological sequelae 5 (83.3%). However, study conducted by De et al. observed that there is no significant correlation between the duration of hospital stay and outcome of AES patients [9].

The significant correlation between GCS scores and AES outcomes in our study aligns with similar observations by De et al. and Basu and Kalamuddin. Lower GCS scores were associated with adverse outcomes, emphasizing the prognostic value of GCS in AES patients [3,9].

Our study highlights a noteworthy association between the duration of hospital stay and AES outcomes. Shorter stays were linked to recovery without sequelae or mortality, while longer stays correlated with a higher incidence of neurological sequelae. This contradicts the findings by De et al., suggesting that the duration of hospital stay may vary in its predictive value across different populations [9].

CONCLUSION

This study underscores the significance of fever and altered sensorium as key clinical indicators of AES. JE remains a major contributor to AES morbidity and mortality in the studied region. The role of age-specific factors, serum sodium levels, and the intricate relationship between TLC and neurological outcomes warrant further investigation. The study supports the use of GCS as a prognostic indicator in AES cases and emphasizes the need for comprehensive strategies, including vaccination programs and enhanced surveillance, to mitigate the impact of AES in affected communities.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the writing of this paper. All authors read and approved the final manuscript.

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