BrainStem Encephalitis Associated with Chandipura in Andhra Pradesh Outbreak

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Summary

Clinical data of 104 hospitalized children during the 2003 epidemic of encephalitis in Andhra Pradesh state was retrospectively analysed to know the clinical profile and risk factors associated with mortality. Fever was the first symptom associated with altered sensorium, seizures, diarrhoea and vomiting. Evolution of illness was very rapid with high fatality (47%). Majority of deaths occurred within the first 24 h of illness due to brainstem involvement. On multiple logistic regression analysis, high-grade fever, absent oculocephalic reflex and Glasgow coma score <7 were found to be significantly contributing to the mortality. Evidence of Chandipura virus was detected in these cases as the etiological agent.

Viral encephalitis remains a major public health problem in almost all the countries. Outbreaks of viral encephalitis have been reported to occur periodically in different parts of India. Various viruses like Japanese encephalitis, measles, herpes simplex virus and enteroviruses have been etiologically linked in various outbreaks of encephalitis. Japanese encephalitis is a major endemic virus in many parts of India including the state of Andhra Pradesh.

An epidemic of encephalitis was reported from the Andhra Pradesh state, India during June–September 2003 which was investigated in detail by National Institute of Virology (NIV), Pune to establish the etiologic agent [1]. The present study consists of retrospectively analysed data to describe clinical profile and assess the risk factors associated with fatality in this epidemic.

This study was carried out at the Government Institute of Child Health, Niloufer Hospital, Hyderabad, A.P, India where cases requiring specialist services were referred from all the affected districts of the state. Cases admitted with acute fever, altered sensorium and seizures were registered for study. Children with prior neurological disorders such as cerebral palsy, epilepsy, febrile convulsions and other CNS infections like Pyomeningitis, Tuberculous meningitis and Cerebral malaria were excluded. The final study group consisted of 104 patients.

For all these cases, clinical, epidemiological, treatment and outcome details were recorded in addition to laboratory data that included viral and serological studies.

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form of papular urticaria, mostly on exposed surfaces suggestive of insect bites were noticed in 12.5% of the cases which disappeared in the next 3–4 days. Gastrointestinal and skin bleedings were found in four cases (3.8%). Three patients (2.9%) had shock without dehydration.

Patients had signs of brainstem involvement such as—absent oculocephalic reflex (48.1%), symmetrical pupillary abnormalities (normal or dilated pupils with loss of light reflex in 43.3%) and respiratory irregularities (central hyperventilation, Biots breathing, intermittent prolonged inspiratory gasps) were found in 15.3%. There were no focal asymmetrical, neurological signs such as hemiplegia.

The results of routine haematological, biochemical and cerebrospinal fluid (CSF) analysis done in most of the cases were within reference range (Table 1) and no significant difference was observed among patients who survived from those who did not. The results of coagulogram which was done for four patients with bleeding manifestations suggested disseminated intravascular coagulopathy (DIC). CT scan (n = 5) and MRI of brain (n = 1) were essentially normal.

Sera of 86 patients were tested for anti-JE antibodies and sera of 72 patients were tested for anti-dengue IgM antibodies at Hyderabad and were found to be negative.

Thirty-three blood samples, eight throat swabs and four CSF samples were sent to NIV, Pune for virological and serological analysis. The viral studies included tissue culture using Vero, MDCK and RD cell lines, Peripheral blood co-cultures, Intra cerebral inoculation in 1-day-old Swiss albino mice and RT-PCR. The isolates were confirmed to be Chandipura (CHP) virus by electron microscopy, quick complement—fixation test using hyperimmune CHP virus antiserum, in vitro neutralization test in vero cells and RT-PCR.

CHP virus was isolated and confirmed in eight cases. In 14 cases, anti-CHP virus, IgM antibodies were detected (Table 2). In one case, both IgM antibodies and PCR were positive. All the samples tested negative for Japanese encephalitis, West Nile, dengue, measles, paramyxovirus, rabies, enterovirus, influenza, corona virus and also mycoplasma at three National Laboratories.

The clinical features of 21 cases (Group A) with CHP virus confirmation (culture/PCR/IgM antibodies) were compared with the remaining 83 cases (Group B) who either tested CHP negative or samples were not available for operational reasons (Table 3). The profile was similar in these two groups on detailed univariate analysis using SPSS software. It indicates possibility of same etiology in all these cases of encephalitis of this outbreak for the reasons—(i) negative viral isolation does not exclude viral infection of CNS [2]; (ii) positive antibody index is not reliably obtained until 1–2 weeks of neurological illness [2] and (iii) in general terms, an epidemic is caused by a single microbial agent. In this outbreak, no other etiological agent was detected.

Evolution of illness from fever to death was rapid with high fatality 47.1% (49/104). Majority of deaths (65%) occurred within 24 h and few deaths (6.6%) after 72 h of illness. The survivors recovered without any neurological sequelae. Case management consisted of standard management protocol for encephalitis excluding steroids.

In the absence of signs of raised intracranial pressure, lateral and central brain herniation altered sensorium could be due to predominantly reticular activating system (RAS) involvement in the brain.

### Table 1

| Parameter | Total tested | Mean (±2SD) | Reference range |
|-----------|--------------|-------------|-----------------|
| Hemoglobin | 83 | 11.09 (8.76–13.42) | 11.5–15.5 gm/dl |
| Neutrophils | 83 | 59.88 (50.79–68.97) | 54–62% |
| Lymphocytes | 83 | 32.01 (22.71–41.32) | 25–33% |
| Total leukocyte count (TLC) | 83 | 8200 (3436–12963) | 4500–11000 Cells/cumm |
| Platelet count | 83 | 2.36 (1.37–3.36) | 1.5–4 lakhs/cumm |
| Serum sodium | 83 | 136.06 (127.36–144.76) | 138–145 mmol/l |
| Serum potassium | 83 | 4.14 (2.96–5.32) | 3.5–5.0 mmol/l |
| Blood urea | 83 | 18.58 (9.04–28.12) | 7–18 mg/dl |
| Serum Creatinine | 84 | 0.89 (0.57–1.21) | 0.5–1 mg/dl |
| Random blood sugar (RBS) | 84 | 102.29 (62.61–141.96) | 60–100 mg/dl |
| Total serum bilirubin (TSB) | 48 | 0.98 (0.75–1.21) | 0.2–1 mg/dl |
| SGPT | 48 | 22.40 (0–45.66) | 5–45 U/l |
| Alkaline phosphatase | 47 | 279.23 (53.27–505.20) | 145–420 U/l |
| Serum Ammonia | 47 | 77.36 (41.96–112.76) | 48–195 Microgram N/dl |
| Cerebrospinal fluid protein | 36 | 30.56 (12.4–48.71) | 15–45 mg/dl |
| Cerebrospinal fluid cell count | 36 | 2.39 (0–6.28) | 0–5 cells/cumm |
brainstem involvement and were found to be phallic reflex and Glasgow coma score (absent light reflex with normal/dilated pupils), respiratory abnormalities (central hyperventilation, apneustic, atactic respirations), absence of oculocephalic reflex and Glasgow coma score (<7) suggested brainstem involvement and were found to be significantly contributing to high mortality. Some of these brainstem signs could be due to raised intracranial tension and brain herniation. But features suggestive of raised intracranial tension such as persistent and projectile vomiting, papilledema, bradycardia and hypertension were absent. Features suggestive of lateral and central herniation signs were also absent. All these observations indicated predominant involvement of brainstem due to viral tropism.

The clinical profile of this outbreak was different from JE in that clinical course was shorter, progression to death was rapid as compared to JE. Although seizures did occur in the initial phase of illness, they were few in number and could promptly be controlled unlike in JE; signs of extrapyramidal involvement characteristic of JE were absent and there was no meningeal involvement; there were no neurological sequelae in the recovered patients [6]; JE virus was not detected in this outbreak either on serology or PCR.

Encephalitis is an unusual manifestation of dengue fever which may occur late in the course of disease [7] unlike in the present epidemic where fever and altered sensorium occurred simultaneously. The presence of bleeding tendencies in four patients and shock in three patients was due to disseminated intravascular coagulopathy (DIC). The shock could also be due to involvement of vasomotor centre in the brainstem.

### Table 2

**Details of CHP viral studies**

| PT no | Age/sex | IgM | POD | IgG | NT | Isolation | PCR |
|-------|---------|-----|-----|-----|----|-----------|-----|
|       |         |     |     |     |    | TS BLD CLOT |     |
| 1     | 5/M     | −ve | 1   | −ve | <10| V/R       | +ve |
| 4     | 4/F     | −ve | 0   | −ve | <10|           |     |
| 5     | 4/F     | −ve | 2   | −ve (SR/CSF) | <10| +ve (V/R/M) | −ve (PB) |
| 7**   | 6/F     | −ve | 1   | −ve (SR/CSF) | 5  | −ve (V/R)   | −ve (PB) |
| 8     | 2.5/F   | −ve | 2   | −ve | <10| −ve (V/R/M) | +ve (PB) |
| 9     | 9/F     | +ve | 8   | −ve | 270|           |     |
| 10    | 11/F    | +ve | 7   | −ve | <10|           |     |
| 11    | 4/M     | +ve | 7   | +ve  | >270|           |     |
| 12    | 4/F     | +ve | 14  | +ve  | >270|           |     |
| 13    | 8/M     | +ve | 0   | +ve  | <10|           |     |
| 14    | 9/M     | −ve | 1   | −ve  | <10| +ve (M)    |     |
| 15    | 11/F    | +ve | 12  | +ve  | >270|           |     |
| 16    | 4/M     | +ve | 10  | +ve  | 270|           |     |
| 17    | 9/M     | +ve | 7   | −ve  | 90 |           |     |
| 18    | 5/F     | +ve | 6   | −ve  | 10 |           |     |
| 19    | 0.75/M  | +ve | 6   | +ve  | >270|           |     |
| 20    | 3/F     | +ve | 5   | +ve (SR/CSF) | 270| −ve (V/R/M) | −ve (PB) |
| 23    | 4/M     | +ve | 7   | +ve (SR/CSF) | 90 | −ve (V/R/M) | −ve (PB) |
| 24    | 5/M     | +ve | 4   | −ve  | <10| +ve        |     |
| 25    | 4/F     | +ve | 8   | +ve  | >270|           |     |
| 32    | 8/F     | −ve | 0   | −ve  | 5  | −ve(V/R)   | ND |

**POD:** Post Admission Day; **PB:** Peripheral blood Co-cultures; **NT:** Neutralization test; **ND:** Not done; **TS:** Tissue culture; **CSF:** Cerebrospinal fluid.
Dengue etiology was ruled out serologically and virologically. Reye syndrome is characterized by biphasic course, absence of fever, moderate hepatomegaly, abnormal liver function tests, hyperammonemia, hypoglycaemia [8–10]. In the present outbreak, all the cases had fever, none showed hepatomegaly or biochemical abnormalities (Table 1). Thus the clinical profile of 2003 epidemic of encephalitis in A.P., India was quite different from the ones reported earlier [6, 8, 10]. It is characterized by rapid evolution of signs and symptoms with

| Clinical feature                      | Group A (21) CHP | Group B (83) | p value | Chi-square | 95% CI       | OR         |
|--------------------------------------|-----------------|--------------|---------|------------|--------------|------------|
| Age                                  |                 |              |         |            |              |            |
| ≤5 years                             | 10 (47.6%)      | 51 (61.4%)   | 0.250   | 1.321      | 0.669–4.596 | 1.753      |
| >5 years                             | 11 (52.4%)      | 32 (38.6%)   |         |            |              |            |
| Sex                                  |                 |              |         |            |              |            |
| Male                                 | 09 (42.9%)      | 50 (60.2%)   | 0.151   | 2.063      | 0.188–1.305 | 0.495      |
| Female                               | 12 (57.1%)      | 33 (39.8%)   |         |            |              |            |
| Nutrition                            |                 |              |         |            |              |            |
| Normal                               | 09 (42.9%)      | 34 (41%)     |         |            |              |            |
| Malnutrition (<3 centile, NCHS)      | 12 (57.1%)      | 49 (59%)     | 0.875   | 0.025      | 0.410–2.848 | 1.081      |
| Fever grade                          |                 |              |         |            |              |            |
| High grade                           | 09 (42.9%)      | 34 (41%)     | 0.875   | 0.025      | 0.351–2.437 | 0.925      |
| Low or mod. Grade                    | 12 (57.1%)      | 49 (59%)     |         |            |              |            |
| Fever (duration)                     |                 |              |         |            |              |            |
| ≤3 days                              | 17 (81%)        | 73 (88%)     | 0.401   | 0.705      | 0.480–6.141 | 1.718      |
| >3 days                              | 04 (19%)        | 10 (12%)     |         |            |              |            |
| Seizure (type)                       |                 |              |         |            |              |            |
| GTCS                                 | 20 (95.2%)      | 60 (72.3%)   | 0.052   | 3.764      | 0.972–60.459 | 7.667      |
| Focal                                | 01 (4.8%)       | 23 (27.7%)   |         |            |              |            |
| Altered sensorium (duration)         |                 |              |         |            |              |            |
| ≤1 day                               | 15 (71.4%)      | 71 (85.5%)   | 0.127   | 2.333      | 0.767–7.306 | 2.367      |
| >1 day                               | 06 (28.6%)      | 12 (14.5%)   |         |            |              |            |
| GIT symptoms                         |                 |              |         |            |              |            |
| Absent                               | 09 (42.9%)      | 27 (32.5%)   | 0.374   | 0.790      | 0.242–1.711 | 0.643      |
| Present                              | 12 (57.1%)      | 56 (67.5%)   |         |            |              |            |
| Skin rash                            |                 |              |         |            |              |            |
| Absent                               | 19 (90.5%)      | 72 (86.7%)   | 0.644   | 0.213      | 0.141–3.376 | 0.689      |
| Present                              | 2 (9.5%)        | 11 (13.3%)   |         |            |              |            |
| Bleeding tendencies                  |                 |              |         |            |              |            |
| Absent                               | 20 (95.2%)      | 80 (96.4%)   | 1.000   | 0.000      | 0.132–13.508 | 1.333      |
| Present                              | 01 (4.8%)       | 03 (3.6%)    |         |            |              |            |
| Shock                                |                 |              |         |            |              |            |
| Absent                               | 20 (95.2%)      | 81 (97.6%)   | 0.565   | 0.331      | 0.175–23.463 | 2.025      |
| Present                              | 01 (4.8%)       | 02 (2.4%)    |         |            |              |            |
| Pupils                               |                 |              |         |            |              |            |
| Normal                               | 12 (57.1%)      | 47 (56.6%)   | 0.966   | 0.002      | 0.388–2.686 | 1.021      |
| Abnormal                             | 09 (42.9%)      | 36 (43.4%)   |         |            |              |            |
| Oculo cephalic reflex                |                 |              |         |            |              |            |
| Present                              | 13 (61.9%)      | 41 (49.4%)   | 0.305   | 1.050      | 0.625–4.436 | 1.665      |
| Absent                               | 08 (38.1%)      | 42 (50.6%)   |         |            |              |            |
| Glasgow coma scale                   |                 |              |         |            |              |            |
| ≤7                                   | 14 (66.7%)      | 54 (65.1%)   | 0.890   | 0.019      | 0.338–2.265 | 0.931      |
| >7                                   | 07 (33.3%)      | 29 (34.9%)   |         |            |              |            |
| Outcome                              |                 |              |         |            |              |            |
| Death                                | 10 (47.6%)      | 39 (47%)     | 0.959   | 0.003      | 0.374–2.543 | 0.975      |
| Recovery                             | 11 (52.4%)      | 44 (53%)     |         |            |              |            |
brainstem involvement leading to high mortality and absence of pleocytosis in CSF. CHP virus was the only etiological agent detected in this outbreak. However, further investigations are needed for broader understanding of pathogenesis and clinical spectrum of the disease should such an unfortunate episode recur.

### Table 4

Bivariate analysis of clinical profile

| Variable                     | Death/Total (%) | OR      | 95% CI      | p-value |
|------------------------------|-----------------|---------|-------------|---------|
| Fever grade                  |                 |         |             |         |
| Low to mod                   | 21/61 (34.4)    | 1       | 1.566–8.071 | 0.002   |
| High                         | 28/43 (65.1)    | 3.555   |             |         |
| Fever days                   |                 |         |             |         |
| > 3                          | 3/14 (21.4)     | 1       | 1.002–14.66 | 0.05    |
| ≤ 3                          | 46/90 (51.1)    | 3.833   |             |         |
| Seizure (type)               |                 |         |             |         |
| Focal                        | 14/24 (58.3)    | 1       | 0.221–1.40  | 0.212   |
| GTCS                         | 35/80 (43.7)    | 0.556   |             |         |
| Altered Sensorium (days)     |                 |         |             |         |
| ≤ 1                          | 46/86 (53.5)    | 1       | 0.047–0.645 | 0.009   |
| > 1                          | 3/18 (16.7)     | 0.174   |             |         |
| Oculocephalic Reflex         |                 |         |             |         |
| Absent                       | 37/50 (74.0)    | 1       | 0.041–0.247 | <0.001 |
| Present                      | 12/54 (22.2)    | 0.10    |             |         |
| GIT symptoms                 |                 |         |             |         |
| Absent                       | 12/36 (33.3)    | 1       | 1.029–5.536 | 0.043   |
| Present                      | 37/68 (54.4)    | 2.387   |             |         |
| Skin rash                    |                 |         |             |         |
| Absent                       | 46/91 (50.5)    | 1       | 0.076–1.137 | 0.076   |
| Present                      | 3/13 (23.1)     | 0.293   |             |         |
| Bleeding tendencies          |                 |         |             |         |
| Absent                       | 45/100          | 1       | 0–1.610     | 0.686   |
| Present                      | 4/4 (100)       | 1639.89 |             |         |
| Pupils                       |                 |         |             |         |
| Normal                       | 17/59 (28.8)    | 1       | 2.583–14.316 | <0.001 |
| Abnormal                     | 32/45 (71.1)    | 6.081   |             |         |
| Shock                        |                 |         |             |         |
| Absent                       | 45/101 (45.5)   | 1       | 0–1.710     | 0.727   |
| Present                      | 3/3 (100)       | 1604.244|             |         |
| Glasgow coma Score           |                 |         |             |         |
| ≤ 7                          | 44/68 (64.7)    | 1       | 0.030–0.256 | <0.001 |
| > 7                          | 5/36 (13.9)     | 0.088   |             |         |
| Vomiting                     |                 |         |             |         |
| Absent                       | 15/42 (35.7)    | 1       | 0.977–4.890 | 0.057   |
| Present                      | 34/62 (54.8)    | 2.186   |             |         |
| Diarrohea                    |                 |         |             |         |
| Absent                       | 27/65 (40.9)    | 1       | 0.884–4.463 | 0.097   |
| Present                      | 22/38 (57.9)    | 1.986   |             |         |
| Malnutrition                 |                 |         |             |         |
| Absent                       | 19/43 (44.2)    | 1       | 0.558–2.677 | 0.616   |
| Present                      | 30/61 (49.2)    | 1.222   |             |         |
| Respiration                  |                 |         |             |         |
| Regular                      | 36/88 (40.9)    | 1       | 1.663–23.555| 0.007   |
| Irregular                    | 13/16 (81.3)    | 6.259   |             |         |

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