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.

The first symptom in these cases was fever with altered sensorium followed by seizures, diarrhoea and vomiting. Fever was continuous and its grade varied from low (102°F) to high grade (104°F) (41.3%) and subsided within 2–3 days from the onset in most of the cases (86.5%). Fever was immediately followed by altered sensorium; its severity varied from patient to patient. Glasgow score was $\leq$7 in 65.4% of the cases and >7 in 34.6% of the cases.

Seizures occurred during initial 1–3 days of illness. They were few and did not recur (GTCS 76.9%, Focal 23.1%).

Diarrhoea and vomiting were present (65.4%) during the first 24 h and were not severe enough to produce dehydration. Skin manifestations in the

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TABLE 1
Hematological and biochemical profile

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/cumn
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

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 2
Details of CHP viral studies

PT no	Age/sex	IgM	POD	IgG	NT	Isolation		PCR		
						TS	BLD CLOT	TS	SR	CSF
1	5/M	−ve	1	−ve	<10	V/R		+ve		
4	4/F	−ve	0	−ve	<10		+ve (PB)			
5	4/F	−ve	2	−ve (SR/CSF)	<10	+ve (V/R/M)	−ve (PB)	+ve	−ve	−ve
7**	6/F	−ve	1	−ve (SR/CSF)	5	−ve (V/R)	−ve (PB)		+ve	−ve
8	2.5/F	−ve	2	−ve	<10	−ve (V/R/M)	+ve (PB)	−ve	−ve	−ve
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)		+ve		
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		−ve
23	4/M	+ve	7	+ve (SR/CSF)	90	−ve (V/R/M)	−ve (PB)	−ve	−ve	
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		+ve	NA

POD: Post Admission Day; PB: Peripheral blood Co-cultures; NT: Neutrilization test; ND: Not done; TS: Tissue culture; NA: Not available; BLD: Blood clot; V/R: Vero/RD; SR: Serum; V/R/M: Vero/RD/MDCK; CSF: Cerebrospinal fluid.

stem rather then extensive cerebral involvement [3]. It is also corroborated by the absence of focal neurological signs, persistent seizures and normal CT and MRI brain.

Cerebrospinal (CSF) pleocytosis was absent in these cases as was also observed in encephalitis due to rabies [4], small pox and influenza [2,5], where it is assumed that the cell metabolism is destroyed because of the activity of pyrogenic and encephalotoxic viral proteins [2]. It could be surmised that a similar mechanism may be operating in Chandipura encephalitis.

By comparing the survived and death cases, it was observed that several clinical symptoms were significantly associated with mortality on bivariate analysis (Table 4). However only high-grade fever (OR = 4.32, CI = 1.23–15.23, $p = 0.023$), absent oculocephalic refex (OR = 0.089, CI = 0.026–0.305, $p < 0.001$) and Glasgow coma score <7 (OR = 0.151, CI = 0.029–0.8, $p = 0.026$) were found to be significantly predicting the mortality on the multiple logistic regression analysing using SPSS for Windows.

Signs and symptoms like pupillary abnormalities (absent light reflex with normal/dilated pupils), respiratory abnormalities (central hyperventilation, apneustic, ataxic 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 3
Comparing the clinical profile of CHP +ve cases (Group A) and others (Group B)

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%)				
>5 years	11 (52.4%)	32 (38.6%)	0.250	1.321	0.669–4.596	1.753
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%)				
Present	01 (4.8%)	02 (2.4%)	0.565	0.331	0.175–23.463	2.025
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%)				
Occulo 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%)				
Out come						
Death	10 (47.6%)	39 (47%)	0.959	0.003	0.374–2.543	0.975
Recovery	11 (52.4%)	44 (53%)				

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

TABLE 4
Bivariate analysis of clinical profile

Variable	Death/Total (%)	OR	95% Cl	*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 (31.9)	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		

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.

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