

## Original Research Article

# Cerebrospinal fluid analysis in dengue in a tertiary care center

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## ABSTRACT

**Background:** Clinical profile of dengue is variable including neurological manifestations like encephalopathy and encephalitis which are not being reported very frequently. This study is an attempt to know the cerebrospinal fluid (CSF) finding in dengue infected patients with neurological manifestations in a tertiary care hospital Eastern Odisha.

**Methods:** Study conducted from August 2018 to July 2019 comprising of 100 dengue seropositive (NS1/IgM/IgG) patients of age >15 years in IMS and SUM Hospital.

**Results:** A total of 100 (66 boys and 34 girls) hospitalised patients (Age >15 years) diagnosed as dengue were enrolled in our study. Total 20 cases Cerebrospinal fluid analysis has been done in which we found 70% (13 cases) unclassified viral meningitis, 15% (3 cases) bacterial meningitis, 5% (1 case) tuberculous meningitis, 5% (1 case) herpes encephalitis and 5% (1 case) Japanese encephalitis. Neurological manifestations in all dengue sero positive cases (100) found 30% headache, 18% altered sensorium, 5% seizure, 4% syncope, 3% papilloedema, 1% CN palsy and 11% meningeal signs.

**Conclusions:** Dengue meningoencephalitis must be thought of in differentials of all febrile encephalopathy. This study brings out the incidence of different meningoencephalitis on the bases of CSF analysis including coinfections. So in dengue patients with neurological manifestation should do CSF analysis for better outcome of a disease.

**Keywords:** Cerebrospinal fluid, Dengue, Headache, Meningeal signs, Meningoencephalitis, Neurological

## INTRODUCTION

Dengue is found in tropical and subtropical areas around the world, predominantly in urban and semi-urban regions.<sup>1</sup> The disease is caused by a virus due to family Flaviviridae that is spread by Aedes mosquitoes.<sup>2</sup>

Some 2.5 billion people two fifths of the world's population in tropical and subtropical countries are at risk and an estimated 50 million dengue infections occur worldwide annually.<sup>3,4</sup>

Dengue and DHF is endemic in more than hundred countries in the WHO regions of Africa, the Americas,

the Eastern Mediterranean, the Western Pacific and east Asia but The South East Asia and Western Pacific regions are the most seriously affected.<sup>4</sup> Epidemics of dengue are rising in frequency. During epidemics, infection rates among those who have not been previously exposed to the virus are often 40% to 50% but can also increase to 80% to 90%.

Some recent reports indicate that the clinical profile of dengue is changing. Neurological manifestations are being reported very frequently. While the actual incidence of various neurological complications is not certain, the reported incidence of encephalopathy and

encephalitis, the most common neurological manifestations of dengue.

From the pathogenesis point of view, neurological manifestations of dengue can be grouped into different categories:

- Related to neurotropic effect of virus (meningitis or encephalitis)
- Related to systemic complication of dengue infection (encephalopathy)
- Post infectious like acute disseminated encephalomyelitis, myelitis, Guillain Barre Syndrome and optic neuritis.

Intra-cerebral hemorrhage may occur as a result of direct tissue lesion caused by the virus, capillary hemorrhage, disseminated intravascular coagulation and increase of hepatic failure. Encephalitis, aseptic meningitis and acute disseminated encephalitis are seen due to neuro-virulent effect of dengue viruses and serotypes 2 and 3 have been isolated from the CSF of these patients.<sup>5</sup> Infiltration of virus laden macrophages can be the possible mechanism. Optic neuropathy is common ophthalmic manifestation and can either recover completely or progress to permanent visual deficit.<sup>5</sup> A rare muscle involvement in dengue can take place in the form of myalgia/cruris and is postulated to be due to direct muscle fiber invasion by dengue virus or release of myogenic cytokine.

Since this hospital is tertiary care hospitals, authors do see a lot of patients with dengue infection, including those with neurological manifestations. So in this communication an attempt has been made to know the cerebrospinal fluid (CSF) finding in dengue infected patients in a tertiary care hospital Eastern Odisha.

## METHODS

This study was a prospective, observational study conducted in department of General Medicine comprising of 100 patients suffering from dengue selected from Indoor of Department of Medicine of IMS and SUM Hospital, a tertiary care hospital, Odisha, during the period from August 2018- July 2019.

### Inclusion criteria

- Patients of more than 15 years of age who had fever and who were found to be positive for NS1 antigen (Micro ELISA) or dengue IgM (antibody) with or without IgG positive for Dengue were included in study.

### Exclusion criteria

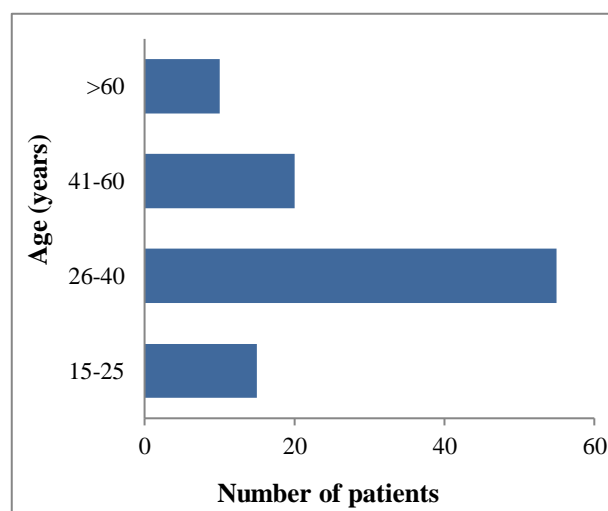
- Any pediatric patients less than 15 years, outdoor patients of dengue, known case of CLD and known case of CKD and known case of CAD.

Total of 100 patients (age >15 years) were included during the outbreak of disease. A detail clinical history, systemic examination routine haematological examination i.e. haemoglobin (Hb)g/dl, total leukocyte count (TLC) cells/mm<sup>3</sup>, platelet count (PC) cell/mm<sup>3</sup>, Liver Function Test (LFT), Renal Function Test (Serum Urea, Creatinine), PT, INR, Stool for Occult Blood, Urine Routine and Microscopy, IgM antibodies for typhoid, malarial antigen Test (MP ICT), slide test for malaria parasite, RBS, Chest X ray PA View, Ultrasonography of Abdomen and Pelvis was performed. Special investigations done to detect co-infections like chikungunya IgM (ELISA), scrub typhus IgM (ELISA), hepatitis B antigen (HbsAg). JE IgM and HSV in CSF. Cerebrospinal fluid (CSF) examination done only in those patients whom platelet count was more than 50000 cell/mm<sup>3</sup> and without bleeding manifestations. Patients who were suffering from diabetes, hypertension and other correlated disease were excluded from this study. All subjects were classified according to WHO guidelines. Thrombocytopenia was taken as platelet count less than 1 lakh/mm<sup>3</sup> and leukopenia as white blood cells (WBC) <5000 cells/mm<sup>3</sup>.

Data were entered and analysed in SPSS version 12 statistical software.

## RESULTS

A total of 100 hospitalised patients (Age >15 years) diagnosed as dengue were enrolled in this study. Maximum number of cases was found in age group 26-40 years that is 55%. Between 41-60 years age group 20%, 15-25 years group 15% and above 60 years of 10% (Figure 1).

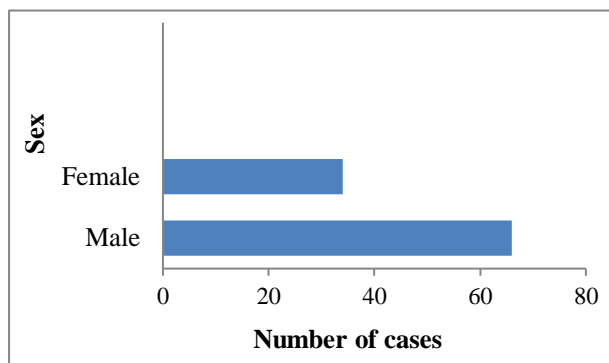


**Figure 1: Age of presentations.**

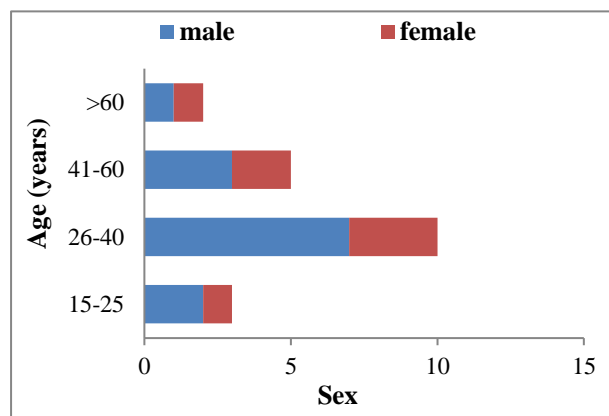
Total of 100 patients (66 boys and 34 girls), who were serologically positive for dengue (Figure 2).

In this series CSF analysis of 20 cases (male 13 and female 7) 50% (10 cases) was in between 26-40 years age, 25% (5 cases) in between 41-60 years age, 15% (3 cases) in between 15-25 years age and 10% (2 cases) above 60 years age (Figure 3).

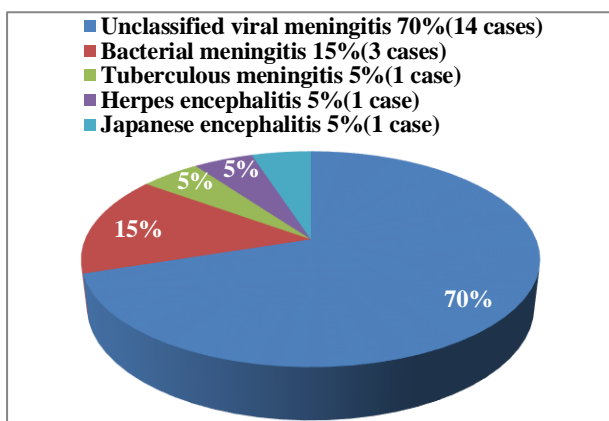
Total 20 cases Cerebrospinal fluid analysis has been done in which authors found 70% (13 cases) unclassified viral meningitis, 15% (3 cases) bacterial meningitis, 5% (1 case) tuberculous meningitis, 5% (1 case) herpes encephalitis and 5% (1 case) Japanese encephalitis (Figure 4).



**Figure 2: Sex in all dengue cases.**



**Figure 3: Age and sex in CSF analysis cases.**



**Figure 4: Classification on the bases of CSF study.**

In this study (20 cases), 14 cases were unclassified viral meningitis, 3 cases were bacterial meningitis, 1 case of tuberculous meningitis, 1 case of herpes encephalitis and 1 case of Japanese encephalitis (Table 1).

In a clinical manifestation of this series (80 case) 100% patient had fever. Myalgia and backache in 75%, rashes 27.5%, vomiting 21.1%, retro orbital pain 15%, abdominal pain 10%, yellowish sclera 5%, oliguria 5% and bleeding manifestations in 55% cases (Table 2).

**Table 1: Classification on the bases of CSF study.**

Classification	Number of patients n=20	%
Unclassified viral meningitis	14	70
Bacterial meningitis	3	15
Tuberculous meningitis	1	5
Herpes encephalitis	1	5
Japanese encephalitis	1	5

**Table 2: Symptoms without neurological manifestations.**

Symptoms	Number of cases (n=80)	%
Fever	80	100
Myalgia and backache	60	75
rashes	22	27.5
Vomiting	17	21.1
Retro orbital pain	12	15
Abdominal pain	8	10
Yellowish sclera	4	5
Oliguria	4	5
Bleeding manifestations	44	55

**Table 3: Neurological manifestations.**

Sign and symptoms	In all cases (n=100)	%	Number of cases (n=20)	%
Headache	30	30	20	100
Altered sensorium	18	18	18	90
Seizure	5	5	5	25
Syncope	4	4	4	20
Papilloedema	3	3	3	15
CN palsy	1	1	1	5
Meningeal signs	11	11	11	55

Neurological manifestations in all dengue sero positive cases (100) found 30% headache, 18% altered sensorium, 5% seizure, 4% syncope, 3% papilloedema, 1% CN palsy and 11% meningeal sign. In 20 cases found 100% (20) cases had headache. Altered sensorium in 90% (18 cases), seizure in 25% (5 cases), syncope in 20% (4 cases), papilloedema 15% (3 cases), CN palsy 5% (1 case) and meningeal signs in 55% (11 cases) (Table 3).

In a 20 cases of CSF cytology WBC count was in the range of 80-550 mm<sup>3</sup>, with mean of 222.4 mm<sup>3</sup>, in viral meningitis 80% (16 cases) mean WBC count was 198.82 mm<sup>3</sup> and bacterial meningitis 15% (3 cases) WBC count mean was 311.33 mm<sup>3</sup>. In differential count 85% (17 cases) were lymphocytes predominant and 15% (3 cases) were PMN predominant, 100% (20 cases) gram stain, CSF culture, ZN stain and CB NAAT were negative (Table 4).

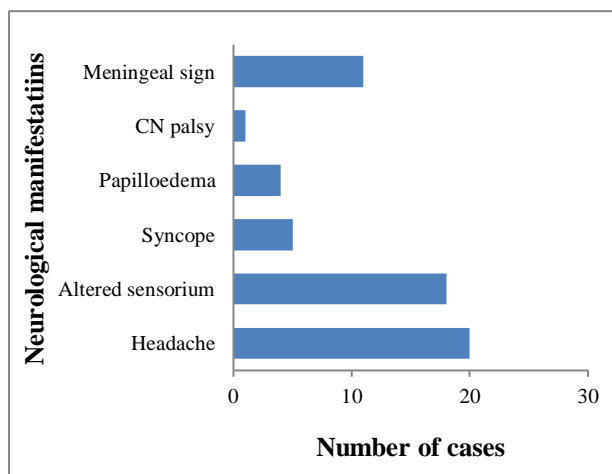


Figure 5. Neurological manifestations in 20 cases.

Table 4: Cytology of CSF.

Case	WBC count <5mm <sup>3</sup>	Differential WBC	Gram stain	ZN stain	CSF culture
1	120	Lymph+++	-	-	-
2	455	PMN+++	-	-	-
3	118	Lymph+++	-	-	-
4	200	Lymph+++	-	-	-
5	400	PMN+++	-	-	-
6	180	Lymph+++	-	-	-
7	225	Lymph+++	-	-	-
8	400	Lymph+++	-	-	-
9	80	Lymph+++	-	-	-
10	350	PMN+++	-	-	-
11	128	Lymph+++	-	-	-
12	135	Lymph+++	-	-	-
13	80	Lymph+++	-	-	-
14	225	Lymph+++	-	-	-
15	550	Lymph+++	-	-	-
16	92	Lymph+++	-	-	-
17	98	Lymph+++	-	-	-
18	400	Lymph+++	-	-	-
19	112	Lymph+++	-	-	-
20	100	Lymph+++	-	-	-

(Lymph+++ Lymphocytes predominantly, PMN+++ Polymorph nuclear leucocyte predominantly, - = Negative).

In this study (20 cases) CSF biochemical analysis found that, 80% (16 cases) appearance of CSF was clear, 15% (3 cases) turbid and 5% (1 case) cob web appearance. Glucose (20 cases) was in range of 15-85 mg/dl, with

mean of 46 mg/dl, viral meningitis 80% (16 cases) mean glucose was 51.8 mg/dl and in bacterial meningitis 20% (4 cases) mean glucose was 21.86 mg/dl. Protein (20 cases) was in the range of 45-122 mg/dl, with mean of 71.5 mg/dl, in viral meningitis 80% (16 cases) mean protein was 65.18 mg/dl and in bacterial meningitis 20% (4 cases) mean protein was 111.75 mg/dl. ADA was in the range of 4-17 IU/L, with mean of 8.2 IU/L (Table 5).

Table 5: Biochemical analysis of CSF.

Case	Appearance	Glucose (40-85 mg/dl) Corresponds glucose	Protein (15-45 mg/dl)	ADA <10 IU/L
1	Clear	50 (90)	60	8
2	Turbid	20 (100)	75	9
3	Clear	52 (86)	45	9
4	Clear	60 (90)	60	8
5	Turbid	25 (102)	122	8
6	Clear	42 (76)	62	11
7	Clear	48 (80)	66	10
8	Clear	66 (103)	70	10
9	Clear	40 (69)	60	8
10	Turbid	30 (110)	102	7
11	Clear	85 (106)	80	7
12	Clear	62 (93)	80	6
13	Clear	52 (96)	84	6
14	Clear	40 (79)	66	7
15	Clear	32 (55)	50	6
16	Clear	43 (75)	50	9
17	Clear	44 (76)	56	6
18	Clear	58 (80)	82	4
19	Clear	56 (82)	72	8
20	Cob-web	15 (89)	88	17

#### MRI scan brain

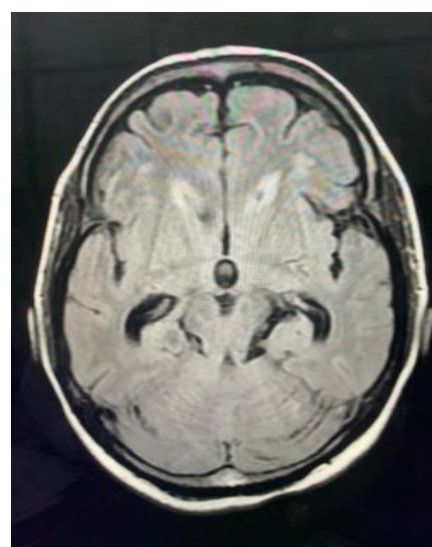
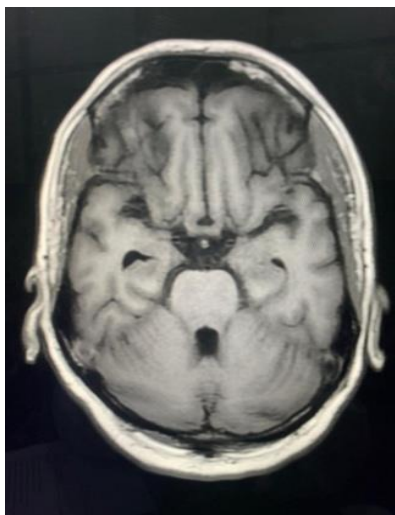
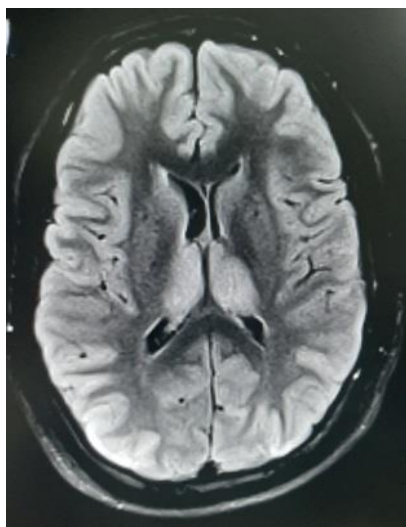


Figure 6: Hyperintense basal exudates with dilated bilateral lateral and 3<sup>rd</sup> ventricles.

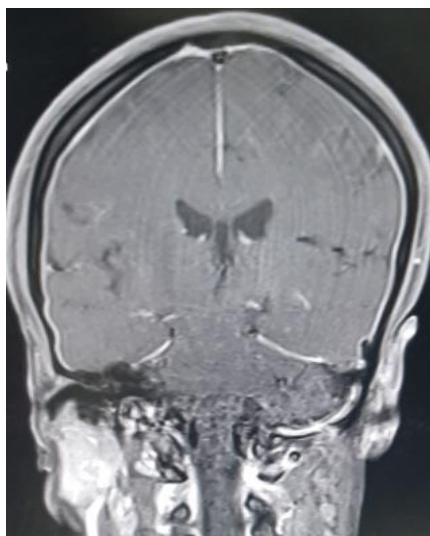




**Figure 7: Enhancement of meninges along pons and 4<sup>th</sup> ventricle.**



**Figure 8: Hyperintense b/l thalamus.**



**Figure 9: Pachymeningeal enhancement.**

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(Figure 6), meningeal enhancements along pons and 4<sup>th</sup> ventricle (Figure 7). In JE patients MRI detected hyper intense b/l thalamus (Figure 8). Some Patients MRI detected Pachymeningeal enhancement (Figure 9). Most of the viral meningitis cases MRI/CECT brain was normal.

## DISCUSSION

Dengue virus infections are among the most common cause for hospital admissions in Eastern Odisha. Presence of neurological manifestations in dengue infection has been recognized for long. In past reports of neurological involvement in dengue infection, the observed 'encephalopathy' was thought to be due to prolonged shock, along with fluid extravasation, cerebral oedema, hyponatremia and liver failure.<sup>6</sup> Recently, direct neurotropic potential of the virus has been detected.<sup>7</sup>

Out of this 100 cases, 30 patients had symptoms and signs pertaining to CNS involvement. Hence, the incidence of neurological involvement in this study was 30%, which authors believe is very high as compared to other studies. The neurological manifestation was 0.5% and 6.2% in the study done by Cam et al, and Hendarito et al, respectively.<sup>8</sup> Authors have detected papilloedema in 15% (3 cases) as in other study authors have detected 0.9% (1 case), reason could be for getting higher number of cases in this study that authors have taken all neurological manifestation cases as in other study authors had taken only ophthalmic manifestations cases.<sup>9</sup>

Authors found 5% (1 case) of CN palsy in tuberculous meningitis patient, it may not be due dengue infection because other studies suggestive of no cranial nerve involvement in dengue encephalitis. Criteria authors used for doing CSF analysis 1) Platelet count >50000 cell/mm<sup>3</sup>, 2) Without any bleeding manifestations. Authors did not do CSF analysis in all 30% cases who were having neurological manifestations because of 2 reasons 1) some of cases had bleeding manifestations and there platelet counts was less than 50000 cells mm<sup>3</sup>, 2) some of cases neurological symptoms was not persisting, like headache was present in 30% (30 cases) but only persisting for 20% (20 cases) rest 10% it was subsided. Because this two reasons authors did CSF analysis in 20% (20 cases) out of 100 dengue seropositive cases. In this CSF analysis, 80% (16 cases) detected picture of viral meningitis, 15% (3 cases) detected bacterial meningitis and 5% (1 case) was tuberculous meningitis. In 80% (16 cases) of viral meningitis 10% (2 cases) authors found IgM JE and HSV in CSF sample. Co-infections could be the reason to getting this type CSF picture, because co-infections in dengue is very common, as seen in recent studies.<sup>10</sup>

In this study, CSF pleocytosis was seen in 100% (20 cases) of the cases, as CSF pleocytosis was seen in 82% of the cases in the studies done by M.L. Kulkarni et al.<sup>11</sup> CSF analysis (20 cases) detected mean WBC count 222.4

cells/mm<sup>3</sup>, along with mean CSF protein of 71.5 mg/dl and with CSF mean glucose 46 mg/dl, which suggest viral invasion into the CNS. Authors excluded JE virus and HSV in CSF but authors should do testing for other viruses also for better outcome. In Early recognition along with meticulous monitoring and targeted supportive treatment is the cornerstone of a successful outcome in dengue meningoencephalitis.

## CONCLUSION

Dengue is a major public health problem in Odisha and surrounding the states of Eastern India. Dengue virus is not classically a neurotropic virus, although there is recent evidence of direct injury neuronal cells. Dengue meningoencephalitis must be thought of in differentials of febrile encephalopathy, and in patients with dengue. This study brings out the incidence of different meningoencephalitis on the bases of CSF analysis and coinfections too. So in dengue patients with neurological manifestation should do CSF analysis for better outcome of a disease. Lacuna of this study was authors did not test for IgM dengue in CSF analysis that authors should in further studies.

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