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Neurological Manifestations of Dengue in a Pediatric Population of a Tertiary Hospital-Niloufer

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Abstract: ***Dengue is a prevailing problem from time immemorial. Various manifestations are reported and updated in journals continuously. Initially, dengue was not considered neurotropic but recent studies conclude otherwise. The neurological manifestations aren't fully studied, as new presentations keep coming up. The neurological manifestations of dengue are studied rarely in the Indian pediatric population and the incidence and presentation are unknown. This infectious disease either presents as asymptomatic cases, dengue with warning signs, severe dengue or expanded dengue syndrome. These cases are identified as other neurological problems and the treatment given is wrong. This study emphasizes the various types of neurological manifestations seen in the dengue pediatric population in Hyderabad in 100 children who presented suggestive of dengue out of which 76 serologically evaluated dengue children varying from the age group of 0-15 years. The incidence of neurological manifestations accounts for 10.5%. The manifestations observed are altered sensorium and generalized seizures. This study emphasizes the need for such studies as early identification can be a life-saving measure for children who are suffering from dengue, early recognition also lowers the cost of treatment for the parents in low-income countries such as India.***

Keywords: Dengue, neurological manifestations of dengue, Indian pediatric population

1. Introduction

Infection with one or more dengue viruses imperils an estimated 2·5 billion people living in tropical and subtropical countries, mostly in large and small cities of the world. Mostly affecting the third-world countries where the population is massive and the mosquito control measures are weak. About 50 to 100 million individuals are infected every year, and in some years as many as half a million people have been admitted to the hospital which is about 10% of estimated going into complications. **(1, 2)** Genetic studies of sylvatic dengue strains provide evidence that the four dengue viruses evolved from a common ancestor in subhuman primate populations and that, around 500 years ago, all viruses emerged separately into a human urban transmission cycle. **(1, 2)**

Almost 20 years ago, dengue virus neurotropism in the human host was considered an opportunistic characteristic. However, more and more evidence strongly supports the notion that the virus is directly neurovirulent detected the dengue virus in the central nervous system (CNS) by assessing viral proteins, ribonucleic acid (RNA), and immunoglobulins found that the dengue virus is highly neurotropic in *Aedesaegypti*. **(3)**

The DENV-2 and DENV-3 serotypes are mostly related to neurological complications. **(3)**

Dengue is a very common disease in the tropical and subtropical regions of the world. It causes a broad spectrum of diseases which can range from subclinical to hemorrhagic fatal forms.

In India, the first epidemic of clinical dengue-like illness was recorded in Chennai in 1780. The first virologically proven epidemic of dengue fever occurred in Kolkata and the eastern coast of India in 1963-64. Dengue is one among the 69 members of the Flaviviridae group of arboviruses name Arbo suggests an arthropod-borne virus which indicates its transmission is from a vector. **(4, 5)** The dengue virus morphology is cubic in structure and comprises of positive single-stranded RNA virus comprising of 4 serotypes namely from 1 to 4. The viruses that cause neurological manifestations are 2 and 3 mainly and 4 to a lesser extent. Incidences are greatest in tropical developing countries where the storage of water is not proper and thus make breeding grounds for Aedes species and rarely albopictus species. **(3, 4, 5)** The largest number of dengue cases in the past decade is noted in 2019 this is partly due to increased reporting of dengue by many states but also to the ever-rising number of dengue cases around the world (world health organization).In the year 2020, an increasing number of cases are noted in India Bangladesh Indonesia etc all comprising, the developing nations. **(6)**

According to WHO about 3.9 billion people are at risk of developing dengue infection and of that 70% of this population resides in Asia. The incidence of dengue presenting as a neurological manifestation is a rare occurrence in the past but now more and more cases are recognized and reported**(6)**

Global strategy: WHO 2012-2020
To reduce the mortality caused by dengue by 50% 2020
To reduce dengue morbidity by 25% by 2020
To estimate the true burden of the disease by 2015**(7)**

From the pathogenesis point of view, the neurological manifestations of dengue infection can be grouped into 3 categories:

Related to the neurotrophic effect of the virus are encephalitis, meningitis, myositis, rhabdomyolysis and myelitis,

Related to the systemic complications of dengue infection: are encephalopathy, stroke (both hemorrhagic and ischemic), hypokalemic paralysis and papilledema.

Post-infection: Acute disseminated encephalomyelitis (ADEM), encephalomyelitis, neuromyelitis optica, optic neuritis, Guillain-Barré syndrome, probable Miller-Fisher syndrome, phrenic neuropathy, long thoracic neuropathy, oculomotor palsy, maculopathy and fatigue syndrome. Encephalopathy: Is the most common neurological manifestation of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), and the pathophysiology is multifactorial and includes cerebral edema, cerebral haemorrhage, hyponatremia, hepatic failure, renal failure, cerebral hypoxia, pathological studies in fatal cases of dengue showed nonspecific lesions such as edema, vascular congestion, focal haemorrhages **(8, 9)**

Aim: To study the various types of neurological manifestations in dengue patients in a pediatric population in a tertiary care centre – Niloufer, Hyderabad.

Objectives

- To understand that neurological manifestations are an important symptom in viral hemorrhagic fevers like dengue.
- To understand the distribution of neurological symptoms in dengue in a pediatric population in a tertiary care centre like Niloufer hospital, Hyderabad.
- To study the initial symptoms and the neurological manifestations in the given population.

Patients and method:
Demographical data was obtained from Niloufer hospital Hyderabad, Telangana during the time of August - September 2020.

100 patients with suspected dengue fever were enrolled in the inpatient department. Serological tests and viral PCR were run on the patients and 76 patients were confirmed with dengue. Only these patients were undertaken for further study.

Inclusion:

- Patients tested positive for the dengue virus both serology and RT-PCR.
- In whom parents gave consent for the study.

Exclusion:

- Patients having chronic systemic illnesses.
- Children with previous neurological disorders, epilepsy.
- Parents who didn't give consent for the study.

Patient history:

History and Clinical examination
Included date of onset of fever/illness symptoms and severity oral fluid intake – quantity and quality urine output - frequency, volume and time of last voiding activities patients can carry out during febrile illness other fluid losses – diarrhoea, vomiting presence of warning signs

Other relevant histories include: family or neighbourhood dengue, travel to dengue-endemic areas, medications (including non-prescription and traditional medicine), jungle trekking and swimming in waterfall - consider leptospirosis, typhus, malaria.

Physical examination included general assessment, mental state, hydration status, hemodynamic status, clinical evidence of warning signs, bleeding manifestations, abdominal tenderness, liver enlargement, fluid accumulation-pleural effusion and ascites.

Other important signs: Tachypnoea/acidotic breathing – indicates shock, rash, tourniquet test - repeat if previously negative or if there is no bleeding manifestation

Laboratory investigations were done:
NS1Antigen IgM and IgG of dengue, RT-PCR for dengue. Complete blood picture, Pt, APTT, INR Liver function test, Renal function test, CSF analysis, EEG and MRI.

2. Results

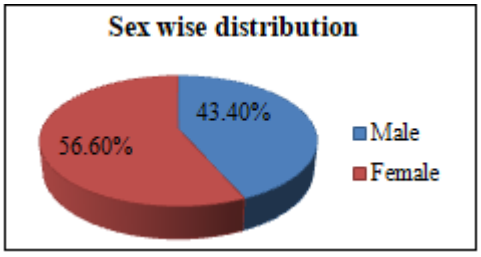
Out of 100 children that showed signs similar to dengue pathophysiology were taken into consideration and out of them 76 children were confirmed with dengue were taken.

Out of which total of 8(10.4%) patients were diagnosed to have a neurological manifestation in our study.

The age wise distribution in male and female population were as follows from 0- 5 years male 19 (46.3 %), female 22 (53.7 %), 6-10 years male 9 (36 %), female 16 (64 %) , and more than 10 years male 5 (50 %) Female 5 (50 %).

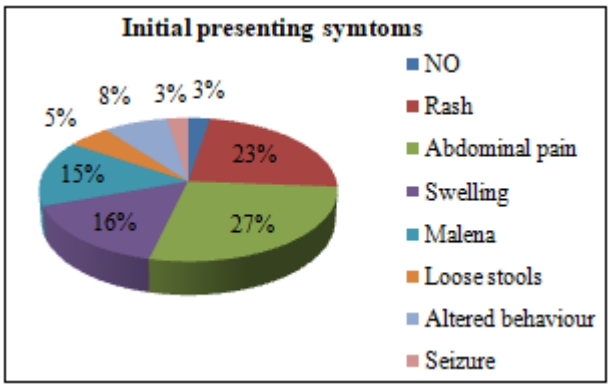
The male and female distribution is 33 (43.4 %) : 43 (56.6 %) with a ratio of 1:1.3 showing a slight female predominance.

Sex	No of Subjects	Percentage
Male	33	43.4 %
Female	43	56.6 %
Total	76	100 %



Initial symptoms the child was bought with as an issue of parent's concern are as follows:

Only fever -2 (2.6%), rash 18 (23.6%), abdominal pain 21 (27.6%), swelling of feet 12(15.7%), melena 11 (14.9%), loose stools 4 (5.2%), altered behaviour 6 (7.8%), seizure 2 (2.6%)



The neurological manifestations depending on the day of the fever:

Less than 2 days from onset of fever the -29 percent, day 2 to day 5 of fever- 55 percent, day 5 to 7 -13 percent.

Fever in Days	0 to 5 Years	6 to 10	>10 Years	Total
< 2 DAYS	14 (63.6%)	7 (31.9%)	1(4.5%)	22 (100%)
2 TO 5	20 (47.7%)	16 (38.1%)	6 (14.2%)	42 (100%)
5 TO 7	5 (50%)	2 (20%)	3(30%)	10 (100%)
>7	2 (100%)	0	0	2 (100%)
TOTAL	41(53.9%)	25 (32.8%)	10 (13.3%)	76 (100%)

Symptoms of neurological manifestation are as noticed by parents:

Altered sensorium in 6 (7.8%) and abnormal movements of the upper and lower limbs in 2 (2.6%) Combined to10.5 percent.

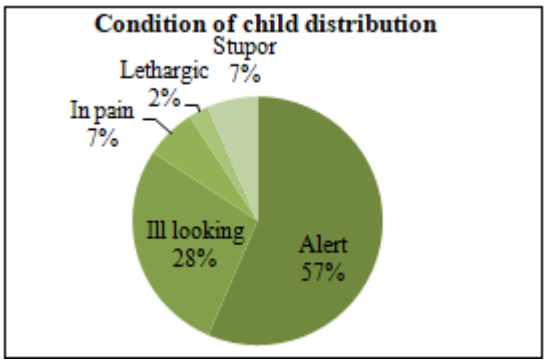
In the 8 cases that showed neurological manifestations, the sex ratio was as follows Male: Female is 2:1.
Condition of the child at arrival is as follows:

Alert 42(55.2%) , ill looking 21 (27.7%) , in pain 5 (6.6%) , lethargic 2 (2.6%) and stupor in 6 (7.8%).

Out of the children admitted for altered sensorium 4 are having a GCS of 9 and the rest 2 a GCS of 7.

The children presenting with seizures had generalized tonic-clonic seizures with loss of consciousness during the episodes no other significant findings were present.

State of Child	*Number*
Alert	43 (56.5%)
ill looking	21 (27.7%)
In pain	5 (6.6%)
Lethargic	2 (2.6%)
Stupor	5 (6.6%)
Irritable cry	0
TOTAL	76 (100%)



The cases were confirmed as dengue serology positive and RT-PCR for dengue.

The lab reports showed mild anaemia and thrombocytopenia ranging from 20, 000+/- 8000 platelets $mm^{3,}$ the liver function tests were deranged in 46 patients, the renal function was deranged in 12 patients with a raise in serum urea and creatinine levels, 54 patients showed increased with a mean of raise been 2-3 times the INR, prolonged PT, APTT time. The tests were done more repeatedly as the disease progressed as intervals guided by the local inpatient settings.

CSF analysis:
Was done on the children who are showing symptoms and signs of neurological manifestations. The reports came out to be mild rise in white blood cell count in 4 children >50 Wbc/mm^3, rest of the cases in the range of 20+/- 2 wbc/mm^3, rest of the values of glucose and protein not showing much deviation from the normal. CSF serology was done for dengue IgM and dengue PCR which came out negative in 7 cases, 1 case got IgM positive for dengue.

Other studies: EEG showed generalised slowing in 3(37.5%) cases that progressed to neurological deterioration.

MRI was normal in all cases.

3. Discussion

Cns and muscle involvement in dengue patients a study from a tertiary care centre written by Usha kand Mishra et al in 2015 in which 116 patients between the age group of 5 to 70 years were taken in which neurological manifestations were present in 92(79%), encephalitis 22% being the most common neurological manifestation [(10)]

Dengue infection presented with central nervous system manifestation by Kankirawatana et al in the year 2000 admitted 44 patients with acute viral encephalitis out of which 8 were diagnosed with dengue infection, the CSF analysis were all normal except one patient in which CSF protein was elevated. In our study, the CSF findings were normal in all samples. [(11)]

Neurological manifestation in dengue patients author pancharoen in June 2001 in Thailand, studied 1493 children out of whom 80 were identified with neurological manifestation an incidence of 5.4% of all dengue patients, encephalitis 42, seizure 35, miscellaneous group 3 which

highly correlated to my findings of encephalitis of 8 patients and 2 of seizure group, we didn't find any other manifestation. [12]

Dengue viral infections as a cause of encephalopathy author Gn Malavige in the year 2007 reported 15 patients confirmed dengue who developed encephalopathy among them 5 patients developed seizures which accounts for 33.3% 2 had generalized seizures and 3 had focal seizures, which is different from our study as our subjects had only generalized seizures. [13]

Dengue infection in patients presenting with neurological manifestation is dengue endemic population by ST Jackson et al 2008 for this study 54 (13%)cases of confirmed dengue were taken out of 401 cases. Clinical manifestations included encephalitis in 28(51.8%) cases , meningitis 18(33.3%) seizures in 6 patients (11.1%) and GBS in 2 patients(3.7%). The majority of our cases had encephalopathy**.** [14]

Neurological manifestations in children with dengue fever: an Indian perspective by Archan et al in year 2016 studied 71 laboratory-confirmed cases, 20 (28.17%) had neurological involvement. Common forms observed were acute encephalopathy (40%), encephalitis (30%), pure motor weakness (15%), transverse myelitis (5%), and acute disseminated encephalomyelitis (5%) and Guillain–Barré syndrome (5%). The dengue IgM antibody could be detected in the cerebrospinal fluid of only two patients with encephalitis, In our study the most common manifestation was encephalopathy and CSF findings in all were normal. [15]

4. Conclusion

In our study, 76 patients had dengue-positive serology which was confirmed with RT-PCR dengue.

8 patients in this population had neurological symptoms accounting for 10.4% which is a significant number.

Out of the 8 patients, 6 had encephalopathy which makes up 75% of the patients suffering from neurological symptoms making it the most common manifestation.

The male is to female =2:1 who suffered from the neurological symptom.

The incidence of neurological manifestations can be anywhere from 0.5% to 20% in some studies.

Recent observations indicate that the clinical profile of dengue is changing, and that neurological manifestations are being reported more frequently. In countries endemic to dengue, it will be prudent to investigate dengue infection in patients with fever and acute neurological manifestations.

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