

ORIGINAL ARTICLE

EVALUATION OF NEUROLOGICAL COMPLICATIONS USING WHO WARNING SIGNS FOR DENGUE DISEASE SEVERITY

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Background: In 2009 a new classification of dengue was proposed by WHO Tropical Disease Research, which classifies dengue into dengue (D), dengue with warning signs (DW) and severe dengue (SD). This classification highlights the warning signs of dengue disease severity. Neurological complications are one of the most serious complications of dengue disease. This study was carried out to see association of neurological complications of dengue patients with WHO warning signs for dengue disease severity, and their outcome. **Methods:** It was a cross-sectional analytical study and included 180 diagnosed and registered cases of dengue hemorrhagic fever. The participants were subjected to a detailed clinical evaluation, laboratory assessment including blood counts, hematocrit, serology for dengue fever and sonography at 24 hours and 48 hours of their admission. **Results:** Twenty-six percent patients were suffering from neurological complications due to dengue. The warning signs for dengue disease severity like altered sensorium (85.5%, $p<0.001$), raised hematocrit ($n=47$, $p=0.029$), gall bladder wall thickening, pleural effusion and ascites on sonographic report ($n=47$, $p=0.024$), were strongly associated with the neurological complications. **Conclusion:** Our study reveals significant association of WHO warning signs for dengue disease severity with neurological complications of dengue disease.

Keyword: Dengue, Neurological complications, WHO warning signs

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INTRODUCTION

Dengue, an acute viral disease transmitted by *Aedes* mosquito, is declared to be endemic in Pakistan by World Health Organization (WHO). It is caused by one of the four serotypes of dengue virus designated as; DENV-1, DENV-2, DENV-3, DENV-4.¹⁻⁴

In 2009 the older classification⁵ used since 1970s was replaced with a new classification of dengue. It was proposed by WHO Tropical Disease Research (TDR) and was published in the WHO TDR 2009 dengue guidelines. This new classification has proven to be useful in clinical management of dengue infected individuals by evaluating the disease severity by the presence or absence of the well

defined signs in the patients suffering from dengue disease, which are termed as 'Warning signs'.⁵⁻⁷

Recent studies hypothesise that the dengue virus is neurotropic. Both direct effect of the virus (neurotropism) and immunological mechanisms caused due to it are responsible for neurological manifestations of dengue infection. However, the exact pathogenesis of the disease has not been established.⁸⁻¹¹

This study was carried out to see association of neurological complications of dengue patients with WHO warning signs for dengue disease severity, and the outcome.

Table-1: Revised WHO classification for Dengue severity⁷

Dengue without Warning Signs	Fever and two of the following signs: <ul style="list-style-type: none"> • Nausea, vomiting • Rash 	<ul style="list-style-type: none"> • Aches and pains • Leukopenia and Positive tourniquet test
Dengue with Warning Signs	Dengue as defined above with any of the following: <ul style="list-style-type: none"> • Abdominal pain or tenderness • Persistent vomiting • Clinical fluid accumulation • Mucosal bleeding 	<ul style="list-style-type: none"> • Lethargy, restlessness • Liver enlargement 2 Cm • Laboratory: Increase in HCT concurrent with rapid decrease in platelet count
Severe Dengue	Dengue with at least one of the following criteria: <ul style="list-style-type: none"> • Severe plasma leakage leading to: <ul style="list-style-type: none"> ▪ Shock (DSS) ▪ Fluid accumulation with respiratory distress • Severe bleeding as evaluated by clinician. 	<ul style="list-style-type: none"> • Severe organ involvement <ul style="list-style-type: none"> ▪ Liver: AST or ALT>1,000 IU/L ▪ CNS: impaired consciousness ▪ Failure of heart and other organs

MATERIAL AND METHODS

This study was carried out by the approval of the institutional ethical committee, Federal Postgraduate Medical Institute, Shaikh Zayed Hospital Lahore, Pakistan, in collaboration with the medical units of Services, Mayo, and Jinnah Hospital, Lahore, respectively from September to November, 2011. It was a cross-sectional analytical study with the sample size of 180 diagnosed and registered patients of dengue hemorrhagic fever.

Upon hospital admission, all the study participants or his/ her next of kin, in case the patient was unconscious, were asked for their written informed consent for participation in this research project. The baseline characteristics, including age, gender, occupation and socioeconomic class, were recorded. A detailed history, clinical evaluation and neurological examination at 24 hours and 48 hours of admission were performed in all the study participants. The muscle power was recorded and noted according to the Medical Research Council grading. We checked the mental status of the unconscious study participants by the

Glasgow coma scale.¹² Routine laboratory investigations including, blood counts, platelet estimation, hematocrit and ultrasonography were performed on each participant.

RESULTS

On central nervous system evaluation, 47 (26.1%) cases were found to be suffering from neurological complications. Among those neurological complications, encephalopathy was the major complication found in 39 (21.7%) cases, meningitis in 2 (1.1%) cases and encephalitis in 1 (0.6%) case.

The comparison of warning signs in dengue patients for dengue disease severity, like alteration of consciousness, ultrasound finding and hematocrit were found significant in relation to the neurological complications ($p < 0.001$, 0.028 and 0.029 respectively) by using Chi-square test (Table-2).

At 48 hours of admission, 92.3% patients with Dengue Shock Syndrome (DSS) recovered and 7.7% patients expired. All the patients who developed DSS were neurologically affected ($p < 0.005$).

Table-2: Comparison of WHO warning signs in Dengue patients with and without neurological complications

WHO Warning signs for Dengue disease severity		Neurological complications		No Neurological complication		p
Variables	Rank	N	%	N	%	
Fever	Afebrile	40	85.1	111	83.5	0.792
	Febrile	7	14.9	22	16.5	
Vomiting	Yes	24	51.1	69	51.9	0.923
	No	23	48.9	64	48.1	
Abdominal pain	Yes	19	40.4	48	36.1	0.279
	No	28	59.6	85	63.9	
Mucosal bleed	Yes	10	21.3	45	33.8	0.108
	No	37	78.7	88	66.2	
Alteration of consciousness	Yes	40	85.1	0	0.0	<0.001*
	No	7	14.9	133	100.0	
Platelet count/mm ³ at 24 hours	≤25	18	38.3	50	37.6	0.648
	26-50	12	25.5	47	35.3	
	51-75	10	21.3	18	13.5	
	76-100	4	8.5	9	6.8	
	100+	3	6.3	9	6.9	
Hematocrit at 24 hours	≤30.0	6	12.8	8	6.0	0.029*
	30.1-40.0	16	34.0	39	29.3	
	40.1-50.0	17	36.2	74	55.6	
	50+	8	17.0	8	9.0	

*Significant

DISCUSSION

This study was carried out to find the association between WHO warning signs for dengue disease severity in dengue patients with and without neurological complications observed for 48 hours of admitted dengue patients with warning signs.

In this study, varied neurological manifestations of dengue infection like encephalopathy, encephalitis, dengue induced Guillain-Barré syndrome, meningitis and dengue shock syndrome were observed to be present in association with WHO proposed warning signs for dengue disease severity. The

WHO warning signs like altered sensorium, pleural effusion, ascites, hepatomegaly and increased hematocrit were significantly associated with these neurological complications.

The exact pathogenesis of the disease has not been established. However, recent studies hypothesize that the virus affects the nervous system.⁸⁻¹¹

Our study results were consistent to the findings of Domingues *et al* who reported involvement of central nervous system in 21.2% dengue patients¹³ and are contrary to Verma *et al* who reported 0.5 to 6% dengue cases with neurological complications.¹¹ Our

results are also consistent with the finding of studies which suggest the neurovirulence of dengue virus.¹⁴⁻¹⁷

Solomon *et al* found alteration of consciousness as the major and most frequently occurring warning sign as reported in our study.¹⁸

Several authors also report gall bladder wall thickening, pleural effusion, hepatomegaly and ascites as common findings on sonography.¹⁹⁻²³

Our study strongly confirmed the neurological manifestation of dengue infection in the population of Pakistan with the presence of warning signs of severe dengue disease.

Neurological involvement plays a vital role in causing significant morbidity and mortality of patients of dengue disease. So, patients with these warning signs should be closely monitored for their early evaluation, management, and better prognosis of the disease.

CONCLUSION

There is a strong association between the neurological manifestations of dengue disease and presence of WHO warning signs of dengue disease severity.

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