Prognostic Indicators for Dengue Infection Severity.

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Abstract

Dengue virus (DENV) infection is arthropod borne infection showing upsurge with rapid urbanization, climate change in India and is a major public health threat.

There is no specific antiviral therapy for dengue infection and treatment of DENV infection is mainly supportive with fluid replacement and antipyretics. The spectrum of disease vary from mild illness as in majority cases to a severe disease course in few cases such as dengue hemorrhagic syndrome, dengue shock, multi-organ failure, and death therefore prompt recognition of severe form is crucial to improve the survival in severe dengue. The underlying cause for severity is not fully understood. Moreover currently, there are no tests available to predict the course of the illness. Therefore, it is imperative to develop an early reliable and feasible clinical symptom to predict the course of dengue illness which can aid in vigorous monitoring and early intervention.

A very crucial observation in our study revealed that pain abdomen, persistent vomiting, bleeding manifestations and edema were significant signs and symptoms in patients of severe dengue with a statistically significant P value (<0.001) implying that these could serve as clinical indicators of severe dengue and help physician to be proactive in management of these cases, thereby reducing mortality. In this study bleeding manifestations were significant with increasing severity.

Further research is needed to explore the underlying patho genetic mechanism in severe dengue, which can lay a foundation for future targeted therapeutic options for combating severe illness.

Keywords: Dengue virus, imperative, patho genetic mechanism.

Introduction

Dengue fever is a common vector borne disease caused by Arbovirus of Flavivirus genus with 4 serotypes and highly prevalent in tropical and subtropical areas and affects about 3.97 billion people across 128 endemic countries including India.

It is Transmitted by Aedes aegypti and Aedes al bo pictus mosquitoes. The severity of illness ranges from are an asymptomatic phase, acute febrile illness, classic dengue fever with or without hemorrhagic manifestation, and dengue hemorrhagic fever (DHF) which includes

Dengue Shock Syndrome (DSS) and expanded dengue syndrome.[1-4]

The common symptoms in patients with dengue fever typically present with the sudden onset of fever, frontal headache, retroorbital pain, and back pain along with severe myalgias also called break-bone fever The additional signs and symptoms includes anorexia, nausea or vomiting, and cutaneous- itching, mobile form rash. In severe illness, epistaxis, gum bleeding, gastrointestinal tract bleeding and rashes are common presentations.[5,6]

The characteristic laboratory finding for the disease is leukopenia along with thrombocytopenia, elevations of serum aminotransferase (SGOT > SGPT).US abdomen study may show GB edema. The diagnosis is confirmed by lgM ELISA or paired serology during recovery or by antigen-detection ELISA or RT-PCR during the acute phase.

Unfortunately there are no specific therapy management of dengue, besides supportive care .[7] The management of viral illness include fluids, rest, and antipyretics.[7] Platelet transfusions is considered in severe throm Bo cytopenia (less than 10,000/cmm) or when there is evidence of bleeding as seen in case of DF/DHF.[8] Volume replacement by immediate administration of intravenous fluids to expand plasma volume is vital and most important in DSS.[6,7,9]

Now a days with urbanization, Dengue fever is still evolving with involvement of newer areas, newer populations and is increasing in magnitude, epidemic after epidemic.[10]

Dengue viral infection remains challenge for the treating physician. So this study was planned to study clinical profile of severe disease in our hospital set-up.

Materials and methods

A descriptive, prospective, cross sectional, analytic study carried out on patients with dengue fever admitted under the Medicine department of SMS hospital, Jaipur, Rajasthan, A tertiary care teaching hospital in north India, during the period of august 2019 to December 2019. The research protocol was presented to the institutional ethics committee (IEC) and approval was taken before commencement of the study.

Inclusion criteria

All new hospitalized patients with classical features of dengue fever with myalgia, headache, rash, bleeding manifestations and thrombocytopenia with positive result of laboratory test (NS1 antigen and IgM & IgG antibody) in SMS hospital Jaipur Rajasthan. Age group 15 years and above were included.

Exclusion Criteria

Patients unwilling to participate in the study, patient who have negative NS1, dengue serology IgM, IgG and documentation of 1 other infectious disease- malaria, urinary tract infection, typhoid fever.

Statistical Analysis

Data thus collected were entered in Microsoft Excel 2016 Worksheet in the form of master chart. These data were classified and analyzed as per the aims and objectives. Qualitative data was expressed in the form of percentage and proportions. Significance of difference in proportions were assessed by Chi-square Test.

To get inferences Primer for Microsoft statistical software version 6 was used and significance set as follows:

P value >0.05 =Not Significant,

P value<0.05 =Significant,

P value<0.001 =High Significant.

Table 1: Correlation of demographic factors with clinical subtypes of dengue (N=210)

Demographic Factor		Dengue without warning Signs	Dengue with warning Signs	Severe Dengue	Total	P-Value*
Age Groups (In Years)	15-25	70	39	11	120	0.450
	26-35	31	13	3	47	
	36-45	13	3	2	18	
	46-55	11	4	2	17	
	> 55	8	0	0	8	
Sex	Male	101	44	8	153	0.018
	Female	32	15	10	57	
Area of Residence	Rural	39	14	7	60	0.437
	Urban	94	45	11	150	

*Chi Square test

In present study it was observed that predominantly 15-25 years old males residing in urban area were most commonly afflicted by various subtypes of dengue fever including dengue fever without warning signs, dengue with warning signs and severe dengue.

Table 2: Correlation of signs& symptoms with clinical subtypes of dengue (N=210)

Sign & Symptom		Dengue without warning Signs	Dengue with warning Signs	Severe Dengue	Total	P-Value*
Headache	Yes	110	47	14	171	0.809
	No	23	12	4	39	
Myalgia	Yes	88	35	9	132	0.331
	No	45	24	9	78	
Retro-orbital Pain	Yes	39	17	7	63	0.689
	No	94	42	11	147	
Persistent Vomiting	Yes	0	8	14	22	< 0.001
	No	133	51	4	188	
Pain Abdomen	Yes	0	19	8	27	< 0.001
	No	133	40	10	183	
Neurological Symptom	Yes	8	3	3	14	0.200
	No	125	56	15	196	
Oedema	Yes	2	28	16	46	< 0.001
	No	131	31	2	164	
Dehydration	Yes	68	30	7	105	0.615
	No	65	29	11	105	

*Chi Square test

Our study also highlighted the fact that persistent vomiting, pain abdomen and oedema correlates with severe dengue fever with a statistically significant p value of < 0.001.

Table 3: Correlation of bleeding manifestations with clinical subtypes of dengue (N=210)

Bleeding Manifestations		Dengue without warning Signs	Dengue with warning Signs	Severe Dengue	Total	P-Value*
Rash/ Petechiae	Yes	14	44	14	72	< 0.001
	No	119	15	4	138	
Conjunctival Suffusion	Yes	57	26	9	92	0.848
	No	76	33	9	118	
Epistaxis	Yes	0	12	6	18	< 0.001
	No	133	47	12	192	
Gum/ Oral bleeding	Yes	0	8	6	14	< 0.001
	No	133	51	12	196	
Hematemesis/ Melena	Yes	0	8	6	14	< 0.001
	No	133	51	12	196	
Haematuria	Yes	0	5	2	7	0.002
	No	133	54	16	203	
Haemoptysis	Yes	2	12	2	16	< 0.001
	No	131	47	16	194	

*Chi Square test

In this sturdy bleeding manifestations were significant with increasing severity.

Discussion

Dengue has been a common febrile illness in the tropics due to a favorable ecosystem for its vector Aedes aegypti in tropical areas.[11] For centuries, the dengue virus has afflicted mankind with illness ranging from mild febrile to life threatening illness. Lately, last few decades have seen dramatic changes in its clinico-demographic profile. Hence, this study aims to highlight these changes observed in a tertiary care center in eastern Rajasthan.

The present study is to comprehensively evaluate the correlation of clinical symptoms/ signs with the develop ment of severe dengue disease (SDD) in patients with DF. The results showed persistent vomiting/nausea, abdominal pain, oedema and bleeding. The factors which were not associated with the disease progression, includes tourniquet positive versus tourniquet negative, gender, lethargy, retroorbital pain, and diarrhea. We found that patients with bleeding after DENV infection had increased risk for progression into SDD (including DHF and DSS).

Probably the progression of DF is mediated by sub neutralizing levels of DENV-specific antibodies which exacerbate the disease by means of an antibody-dependent enhancement of infection (ADE) which induces a complicated immuno patho genesis in the host.[12] The vascular permeability is exaggerated as a

result of ADE in patients with SDD as well as there occurs alterations of endothelial cells and throm bo cytopenia and coagulation disorders.[13] These significant symptoms/ signs, especially the bleeding in form of hematemesis/ melena and hepatomegaly are manifested in patients with SDD as a result of the aforementioned alterations. The *in vivo* model for ADE-induced SDD have shown gastrointestinal bleeding and increased viral RNA in the liver.[14] The skin biopsies shown the deposition of IgM, beta 1 C-globulin, dengue antigen, and fibrinogen deposits within or about blood vessel walls of dermal papillae or in the blood vessels implying that skin rashes that appeared in DHF were caused by an immunopathologic process.[15] Therefore the host immune system plays a pivotal role in triggering symptoms like bleeding, hepatomegaly, and skin rashes, in patients with SDD, which could be used to triage patients in need of intensive care.

The most significant and crucial observation in present study revealed that pain abdomen, persistent vomiting, bleeding manifestations and edema were significant signs and symptoms in patients of severe dengue with a statistically significant p value (<0.001) implying that these could serve as clinical indicators of severe dengue and help clinicians to be proactive in management of these cases, thereby taking proactive steps timely and reducing mortality.

Limitations These observations cannot be generalized due to various limiting factors such as limited sample size and restriction of cases to enrolled hospitalized population only. Therefore, further studies are warranted before any confirmative conclusion can be drawn.

Summary and conclusion

Dengue is the most common vector born infection in the world and predominant cause of tropical infectious crisis. Red flag signs such as persistent vomiting, abdominal pain, bleeding manifestations such as conjunctival suffusion, petechiae, gum bleed, epistaxis, menorrhagia, melena, hematemesis etc. edema, elevated transaminase, pleural effusion or ascites could be used as predictors of severe dengue. Further research is still warranted in correlating the significance of various other clinical and laboratory parameters such as periorbital puffiness, hematocrit and IPF in predicting the severity of dengue. An enhanced knowledge of demo graphic, clinical features and laboratory data will help budding physician and practitioner in periphery to identify early cases of severe dengue and refer them to tertiary centers in nick of time. This will probably help curb down morbidity and mortality due to this very much treatable infectious disease.

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