Relation of Proteinuria with Severity of Dengue Fever

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Abstract

Introduction-When a susceptible host is infected, the symptoms start after an incubation period of 3 to 14 days. The mosquito gets infection from the infected host when it feeds on the host. There is a global resurgence of Dengue fever as a result of population explosion, unplanned urbanization as well as due to lack of effective mosquito control measures. The Dengue virus is transmitted by the Aedes mosquito. Since the early 20th century when experiments showed that Dengue virus was transmitted by Aedes Aegypti.The **Aim** here is to assess the relation of proteinuria with severity of Dengue Fever. The **method** that we have adopted for our researchresearchis Hospital-based Cross-sectional Observational Study. The Study duration was 18 months (1st October 2018 to 31st March 2020). **Result** indicate significant association was seen in occurrences of abdominal pain, nausea, joint pain, edema and altered sensorium in Dengue patients at the earliest for detecting the severity of Dengue and to avoid any further complications related to renal involvement in Dengue.

Key word: Proteinuria, Dengue fever, Abdominal pain, Nausea, Joint pain

Introduction

When a susceptible host is infected, the symptoms start after an incubation period of 3 to 14 days. The mosquito gets infection from the infected host when it feeds on the host. After entering the mosquito, Dengue virus takes an additional 8 to 12 days incubation period and then only the mosquito can transfer the disease to another human. The infected mosquito remains infected for a life time.[1]

There is a global resurgence of Dengue fever as a result of population explosion, unplanned urbanization as well as due to lack of effective mosquito control measures. The development of shock in Dengue can be prevented by diagnosing Dengue early and replacing lost plasma with crystalloids. Sometimes, predicting impending complications like bleeding and shock is difficult owing to absence of classical signs and symptoms of Dengue. The management of such cases and their subsequent outcome depends on early prediction of these complication.[2]

Vector for Dengue

The Dengue virus is transmitted by the Aedes mosquito. Since the early 20th century when experiments showed that Dengue virus was transmitted by AedesAegypti. Although there are various potential vectors for Dengue, the epidemiological experiments proved that AedesAegypti&AedesAlbopictus are vectors in majority of Dengue cases. AedesAegypti is currently distributed in urban areas of tropical regions of Africa, Asia, Australia, South Pacific, America& Middle East. This AedesAegypti has two sub-species named Aedesaegyptiformosus&Aedesaegyptiaegypti. While, Aedesalbopictus (Skuse), better known as the "Asian tiger mosquito", originates in Orient and serves as a secondary vector of DF. These Aedes mosquito Larvae breed from a wide variety of natural and artificial habitats such as bamboo stumps, tree holes, discarded tires and flower vases. AedesAegypti mostly have distribution in tropical region &AedesAlbopictus distributed from tropical to temperate region indicating the south-north gradient geographic distribution difference.[3]

Transmission of Disease

Dengue Fever transmits by the bite of infective female Aedes mosquito. There are some important transmission cycles but, for public health purpose is the urban endemic/epidemic in large urban area. The viruses are maintained in A.aegypti-Human-A.aegypti cycle having periodic epidemic. Aedes is the fearless day biter. The female mosquito only bites & sucks the blood meal.

The transmission of Dengue Fever have upsurge in July to November. Thus, the disease appears in great quantity after the monsoon and do not have uniform distribution throughout the year. But, the Southern & Northern states show perennial transmission.[4]

Aim

To assess the relation of proteinuria with severity of Dengue Fever

OBJECTIVES

• To correlate proteinuria with thrombocytopenia and clinical parameters of disease severity among adult Dengue infected patients

• To find the predictive value of dipstick proteinuria in severe Dengue Fever

• To find the association between proteinuria and various parameters pertaining to disease severity in Dengue Fever

Methods

The Study Design for the present research is Hospital-based Cross-sectional Observational Study. WHO Fact Sheet of 13th September 2018 estimates 390 million dengue infections yearly. 96 million of them presented clinically with severe disease. Hence, the prevalence of severe disease in Dengue infected cases in 2018 was 24.6%.[5] The rsearch has been carried out in Department of Medicine, Krishna Hospital, Karad, Maharashtra. The present study was approved by the Ethics and Protocol Committees of KIMSDU Karad. The written and informed consents from the patients and their relatives were obtained according to ICMR Consent Proforma, before enrolling the patients in the study.

Study duration – 18 months (1st October 2018 to 31st March 2020)

Ethical Committee clearance - Protocol Number 0249/2018-2019

Inclusion Criteria -

Dengue infected patients which include all adults (age >18 years) with documented Dengue NS1 Antigen and/or Dengue IgM Antibody positive status, and who gave consent for the study.

Exclusion Criteria -

1. Patients having known or newly detected comorbidities like diabetes, hypertension, kidney disease, heart disease, neurological disorders or endocrinopathies, or other documented concomitant infections like Malaria, Chikungunya, Leptospirosis, H1N1 or Tuberculosis.

2. Pregnant females, patients with urinary tract infection, trauma patients, patients with malignancy, patients on long term oral or injectable drugs and patients who had fever of more than 2 weeks duration

3. Patients less than 18 years of age, and who did not give consent for the study.

Sampling technique - Simple random sampling

Study population - Patients, both male and female who were Dengue NS1 Antigen positive and/or Dengue IgM positive, and were admitted in Krishna Hospital were included in this study.

Patients with suspected or probable Dengue Fever were admitted in Krishna Hospital under Medicine Department in General Wards and ICUs as per a preliminary clinical assessment in OPD or Emergency Department based on their presenting symptoms and vital signs. The socioeconomic status of the patients were ascertained with the help of Modified Kuppuswamy scale.[6]

Detailed history was taken daily for symptoms like headache, retro-orbital pain, cough, myalgia, joint pain, nausea, vomiting, pain abdomen, diarrhoea or constipation. During the hospital stay, their vital signs were monitored at regular intervals. Temperature was measured with mercury thermometers four times a day as well as whenever the patients complained of fever, and records were kept to find the number of fever spikes per day, the highest temperature recorded during hospital stay and the duration of fever. Blood Pressures were recorded manually with sphygmomanometers twice daily in General Wards and every two hourly in ICUs, and records were kept to kind the lowest systolic and diastolic BP recorded during Hospital stay. They were examined twice daily for evidence of rashes, petechiae, ecchymoses, gum bleeding, epistaxis, hematemesis, malena, hematuria, edema or altered sensorium. Tourniquet test was performed once daily.

Result

This study was conducted on 75 patients diagnosed with Dengue under Medicine Department. Most common age group was 21 to 30 years with 27 cases (36.0%) followed by less than 20 years with 13 cases (17.3%) and 41 to 50 years with 10 cases (13.3%).There were 46 females (61.3%) and 29 males (38.7%) in this study. Female to male ratio was 1.58: 1.Majority of the participants belonged to lower middle class with 37 cases (49.3%), followed by upper middle class with 22 cases (29.3%).In this study, majority of the participants, that is, 59 cases, had mixed diet, followed by rest 16 cases who were vegetarian (21.3%)Among the 75 participants, 69 were Hindu by religion (92%) followed by 4 Muslims (5.3%) and 2 Christians (2.7%).There were 64 patients (85.3%) of DF, 6 patients (8%) of DHF and 5 patients (6.7%) of DSS.Significant association was seen between mean duration of hospital stay, number of fever spikes, highest temperature, lowest BP recorded and presence of proteinuria (p < 0.05).

Significant association was seen in occurrences of abdominal pain, nausea, joint pain, edema and altered sensorium in Dengue patients with proteinuria. (p<0.05)Out of those 29 without proteinuria, only 8 had pain in abdomen (27.6%) and out of 46 cases of proteinuria, 25 had pain in abdomen (54.3%). Out of those 29 without proteinuria, only 13 had nausea (44.8%) and out of 46 cases of proteinuria, 34 had nausea (73.9%). Out of those 29 without proteinuria, only 16 had joint pains (55.2%) and out of 46 cases of proteinuria, 36 had joint pains (78.3%).Out of those 29 without proteinuria, only 5 had edema (17.2%) and out of 46 cases of proteinuria, 21 had edema (45.7%).Out of those 29 without proteinuria, only 1 had altered sensorium (3.4%) and out of 46 cases of proteinuria, 7 had altered sensorium (15.2%).Significant association was seen between proteinuria and bleeding mmanifestations (p<0.05).Out of 32 patients with

rashes, 24 had proteinuria (75%). Out of 15 patients with petechiae, 12 had proteinuria (80%). Out of 8 patients with Ecchymosis, 6 had proteinuria (75%). There was significant difference in dipstick proteinuria among patients of DF, DHF and DSS (p < 0.001). Among the 64 patients of DF, 28 had no proteinuria (43.8%), 21 had trace (32.8%), 13 had +1 (20.3%) and 2 had +2 (3.1%). Out of 6 patients of DHF, 1 had no urine albumin (16.7%), 3 had +1 (50%),1 patient each had +2 (16.7%) and +3 (16.7%). Out of 5 patients of DSS, 2 had +1 (40%), 2 had +2 (40%) and 1 had +3(20%). Significant correlation was seen between TLC and Platelet counts with proteinuria (p < 0.05). Both TLC & Platelet counts were significantly lower in patients with proteinuria. There was significant difference in TLC and Platelets and severity of dengue (p < 0.05). Mean TLC in DF cases was 5035.93, in DHF it was 4133.33 and in DSS it was 30425.04.

There was no any difference in mean Hb values and severity of Dengue (p=0.40).Significant association was found between the urine albumin levels and patient outcome (p < 0.001).All 29 cases with nil urine albumin were discharged (100%). There was one death out of 21 cases with trace urine albumin (4.8%). There were 2 deaths amongst patients with +1 urine albumin (9.5%). There were 3 deaths amongst patients with +2 urine albumin (60%). Both patients with urine albumin +3 had died (100%).No significant difference was seen in presence of proteinuria between patients with NS1Ag and IgM positivity. (P > 0.05).

Discussion

Patients having known or newly detected comorbidities like diabetes, hypertension, kidney disease, heart disease, neurological disorders or endocrinopathies; pregnant females, patients with other concomitant documented infections like Malaria, Chikungunya, Leptospirosis, H1N1 or Tuberculosis, urinary tract infection, trauma patients, patients on long term oral or injectable drugs, patients with malignancies and fever of more than 2 weeks duration were excluded.

The findings of the present study were similar to the observations in studies conducted by ShaistaChoudhary et al and Prathyusha et al.[7,8] The mean age of distribution was 23.13 years.

In the present study, there were 46 females (61.3%) and 29 males (38.7%) in our study. Female to male ratio was 1.58: 1. The findings were similar to the study by Fransisca RF et al with respect to proportion of females (53.25%) and males (46.5%).

Majority of the participants were lower middle class 37 (49.3%), followed by upper middle class with 22 cases (29.3%). In our study, majority of the participants had mixed diet, 59 cases (78.7%) followed by

rest 16 cases who were vegetarian (21.3%) 69 cases were Hindu by religion (92%) followed by 4cases Muslim (5.3%) and 2 Christians (2.7%).

The dengue cases were classified as per criteria by WHO (1997), into DF, DHF and DSS. In the present study, 64 cases (85.3%) had DF, 6 cases had DHF (8%) and 5 cases had DSS (6.7%).

This was almost correlating with the studies conducted by B Rezeki et al (67.1%) and Carlos CC et al (66.66%).[9,10]

The occurrence of DSS when compared with the study of Kumar et al (7.3%) had a good correlation while DHF when compared with the study of Celia CC et al 9 had increased number of cases (33.4%).[11]

Mean lowest systolic BP recorded was significantly less in Dengue Shock Syndrome, 82.14 ± 16.52 mmHg as compared to Dengue Hemorrhagic Fever

 96.66 ± 8.16 mmHg and Dengue Fever 102.18 ± 14.19 . (p=0.024) Mean lowest diastolic BP recorded was significantly less in Dengue Shock Syndrome, 58.07 ± 13.25 mmHg as compared to Dengue Hemorrhagic Fever 67.0 ± 7.87 mmHg and Dengue Fever 64.21 ± 14.23 . (p=0.013)

In the present study, significant difference was seen between the pain in abdomen, nausea, joint pains, edema and altered sensorium in dengue patients with proteinuria. (p<0.05) Significant difference was seen in mean duration of hospital stay, number of fever spikes, highest temperature, lowest BP recorded & presence of proteinuria (p < 0.05). There was significant difference in the presentation of Dengue shock syndrome, Dengue Hemorrhagic Fever and Dengue fever patients with regards to pain in abdomen, Vomiting, Edema and Altered sensorium. (p<0.05)

Faiz Ahmed Raza et al reported headache, myalgia and vomiting as the commonest symptoms amongst both DF and DHF patients with no significant difference between them.[12] The occurrences of abdominal pain, abdominal tenderness, splenomegaly, hepatomegaly, nausea, rash, spontaneous hemorrhage and periorbital puffiness were significantly (p<0.05) associated with DHF. Retro-orbital pain was found more in DHF, but the finding was not statistically significant.

There was significant difference in the presentation of Dengue shock syndrome, Dengue Hemorrhagic Fever and Dengue fever patients with regards to bleeding tendencies in terms of rashes, Patechiae, Ecchymosis, Malaena, Hematuria, Epistaxis, Hematemesis and Positive Tourniquet Test (p < 0.05). Bleeding tendencies were seen more in Dengue shock syndrome and Dengue Hemorrhagic Fever patients.

Farhad F. Vasanwala et al studied the value of proteinuria in predicting the development of DHF. They found DHF patients (85%) having significantly higher peak levels of proteinuria than DF patients (61%) with cut-off value of UPCR being equal to or more than 20 mg/mmol.[13]

It is postulated that the NS1 antigen of Dengue virus gets attached to heparansulphate molecule of glycocalyx, leading to alteration in its filtration and consequent proteinuria and hypoalbuminemia.[14]

It is postulated that Dengue infection results in coagulopathy and complement activation, which leads to more consumption of platelets and their peripheral sequestration.[15] In secondary Dengue infections, macrophages have been demonstrated to engulf platelets in vitro by unknown mechanisms. [16] Antibodies of IgM type against platelets were found in Dengue patients, with higher titres in DHF and DSS patients, and higher cytotoxicity when complement activation occurred. [16]

Conclusion

Dengue is one of the deadliest infectious disease prevalent in developing countries like India. It is very important to evaluate patients early for the severity of dengue fever and any possible complications of Dengue in them. In the present study, presence of proteinuria was associated with Dengue Hemorrhagic Fever and Dengue Shock Syndrome compared to Dengue Fever. The presence of incremental trend of proteinuria was associated with longer duration of hospital stay, more frequent fever spikes and low mean blood pressure. The increase in quantity of proteinuria was negatively correlated with platelet count. The study concludes that it is important to look for proteinuria in Dengue patients at the earliest for detecting the severity of Dengue and to avoid any further complications related to renal involvement in Dengue.

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