Original Article

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Correlation of Muco-Cutaneous Lesions with Severity of Dengue Fever in Children

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Abstract

Background: Infection by one dengue serotype provides lifelong immunity to that particular virus, but other serotypes have no cross protective immunity. Humans and mosquitoes are the principal hosts of Dengue virus; the mosquito remains infected for life but is known to cause illness only in humans. The virus transmitted by bites of Aedes mosquito. **Subjects and Methods:** Informed consent was taken from parents before enrolling in study. A clinical history, physical examination and relevant baseline investigations were done for all the cases. Patients were monitored for development of cutaneous and mucosal manifestations. A pre-structured proforma, which include demographic details of the patient, severity of illness, various mucosal and cutaneous manifestations and day of occurrence of the same, was used to record the clinical data and laboratory parameters from cases selected for the study. **Results:** Dengue fever was classified based on WHO guidelines 2012 into three categories, Dengue Fever without warning sign, Dengue Fever with warning sign and Severe Dengue. Out of 174 cases of Dengue Fever without warning Signs, 114 cases developed mucocutaneous manifestations i.e. 65.52%. Out of 89 cases of Dengue Fever with warning signs, 55 developed Mucocutaneous Manifestation ie 73.33% and out of 47 cases in Severe Dengue group, 42 cases developed Mucocutaneous Manifestations i.e. 89.36%. **Conclusion:** Mucoccutaneous Manifestations were more commonly seen in Severe Dengue compared to Dengue fever with warning signs and Dengue fever without warning signs which was statistically significant (p value < 0.05).

Keywords: Correlation, Muco-cutaneous lesions, Severity of Dengue fever.

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Introduction

Dengue viruses are small spherical single stranded RNA viruses with a lipid envelope belonging to genus flavivirus and family flaviviridae. The viral genome encodes three structural proteins [Capsid protein(C), membrane protein (M), and envelope glycoprotein (E)] and seven nonstructural proteins (NS1M NS2a, NS2b, NS3, NS4b and NS5). The amino acid sequences of the E proteins determine the antibody neutralizing activity that classifies DENV into 4 serotypes: (1) DENV-1 (2) DENV-2 (3) DENV-3 and (4) DENV-4. The E protein also interacts with cellular receptor(s) which initiates viral entry. Each DENV serotype has been classified into genotypes on the basis of sequence data from the E gene or from the junction of the E and NI genes.[1]

Nonstructural proteins of DENV function in RNA replication and assembly and in viral protein processing. Some nonstructural proteins can also modify the host immune system and can influence type 1 interferon signaling and induce cytokine production. NS1 is the only nonstructural protein with a soluble form that can be detected in circulation.

Infection by one dengue serotype provides lifelong immunity to that particular virus, but other serotypes have no cross protective immunity.[2] Humans and mosquitoes are the principal hosts of Dengue virus; the mosquito remains infected for life but is known to cause illness only in humans. The virus transmitted by bites of Aedes mosquito.

In human, each of four dengue virus serotypes has been associated with DF and DHF. DSS occurs with higher frequency in two immunological defined groups i.e. Children who have experienced a previous dengue infection, and infants with weaning levels of maternal dengue antibody.[3]

After a person is bitten by the infected mosquito, the virus remains in that person for 3-14 days and later the person may experience fever. The virus may circulate in the blood during this period of minimum 2 days or maximum 10 days. If any other A. aegypti mosquito bites this infected person in this period then they will carry the same virus and infect other people, with the incubation period of 8-12 days. Compared with uninfected mosquitoes, infected ones take longer to complete a blood meal. This may contribute to the efficiency of A. aegypti as a dengue viral vector. This increased time corresponds to dengue virus infection of organs known to control or influence activities associated with feeding.[4]

The primary (first) dengue infection produces monotypic

antibody to the infecting virus serotype and produces lifelong immunity to the infecting serotype. Subsequent infection with a heterotypic serotype, however, produces a massive anamnestic antibody response, with very high antibody titres that cross-react with all four virus serotypes, as well as with other flaviviruses. The transmission of dengue virus from infected human to feedingmosquitoes is determined by the magnitude and duration of viraemia in the human host; person with higher viraemia provide a higher infection dose for virus to the feeding mosquito leading to a great percentage of feeding mosquitoes becoming infected though even very low levels of virus in blood may be infectious to some vector mosquitoes.[5]

The pathophysiological mechanisms underlying the capillary leak are ill understood. Many factors including total virus burden, viral virulence, host immune response and genetic predisposition have been implicated in the pathogenesis of Severe Dengue, but the means by which any of these factors might influence endothelial function remain unclear. Although increase in microvascular permeability has been well documented using strain gauge plethysmography, suggestive of endothelial dysfunction. However, there is no evidence that the virus directly infects endothelial cells in vivo, and no structural endothelial abnormalities have ever been demonstrated.[4]

Luminal surface of the vascular endothelium has a layer of glycocalyx. Layer incorporates into it glycosaminoglycans which are complex, negatively charged polysaccharides. This layer creates a size selective physical barrier which allows the going of only some molecules between the fibres and an electrostatic barrier which works as a boundary for the access of negatively charged molecules underlying the cellular transport mechanisms. More than the endothelial cellular structures, it is the glycocalyx that shows the perm selectivity. A recent research has pointed a change in the function of the endothelial glycocalyx at the time of dengue infection. The selective limitation on the negative charge is clearly impaired while on the other side the general size-dependent sieving mechanism is partially retained.[6]

Subjects and Methods

The study was conducted over a period of two years on Dengue cases in Paediatrics department of Medical College and Research Hospital. The Study subjects were children with fever of acute onset, with clinical featuressuggestive of Dengue fever as described in WHO 2012 Guidelines.Informed consent was taken from parents before enrolling in study. A clinical history, physical examination and relevant baseline investigations were done for all the cases. Patients were monitored for development of cutaneous and mucosal manifestations.A pre-structured proforma, which include demographic details of the patient, severity of illness, various mucosal and cutaneous manifestations and day of occurrence of the same,was used to record the clinical data and laboratory parameters from cases selected for thestudy. The patients were managed according to WHO protocol.

Inclusion Criteria

Children with age less than 18 years, admitted as Dengue feverbased on clinical features as described in WHO 2012 Guidelines and positive Ns1Ag and/or Dengue IgM.

Exclusion Criteria

- Children who cannot be followed up till 7 days.
- Mucocutaneous changes due to drugs or blood transfusion.
- Children with pre-existing diseases on Chronic medications.
- Children with pre-existing skin diseases.
- Children with dengue fever associated with other illnesses. example: chikungunya, malaria, typhoid, etc .

Results

Table 1: Age Wise Distribution of Dengue Feverwith and Without Mucocutaneous Manifestations

Age in Years	No of Dengue Cases	No of Dengue Cases with Mucocutaneous Manifestation	Percentage of Dengue Cases with Mucocutaneous Manifestation
0-5	65	40	61.54
6-10	99	77	77.78
11-15	85	56	65.88
16-18	47	38	80.85

Dengue cases were further grouped into four categories of age group 0-5yrs,6-10yr,11-15yr, 16-18yr. 65 cases were in age group of 0-5 yrs. 40 cases out of these 65 cases i.e (61.54%) developed mucocutaneous manifestation. Out of 99 cases in the age group of 6-10yrs,77 cases developed mucocutaneous manifestation (i.e.77.78%). In the age group of 11-15yrs, out of 85 cases 56 cases developed mucocutaneous manifestations (ie 65.88%). Out of 47 cases in the age group of 16-18yes, 38 cases (i.e 80.85%) developed mucocutaneous manifestations. Mucocutaneous manifestations were more commonly observed in the age group 16-18yrs i.e. 80.85% followed by age group of 6-10yrs i.e 77.78%. There is no significant diffrence over the age groups with respect to mucocutaneous manifestation (p value >0.05).

Table 2: Sex Wise Distribution of Dengue Fever Cases with Andwithout Mucocutaneous Manifestations

	No of Dengue Fever Cases	No of Dengue Fever Cases with Mucocutaneous Manifestations	Percentage of Dengue fever Cases with Mucocutaneous Manifestations
Male	175	115	65.71
Female	121	96	79.34
Total	296	211	

Of 296 cases, 175 were males and 121 were females . 115 males out of 175and 96 females out of 121 developed mucocutaneousmanifestation.Mucocutaneous manifestations

in dengue fever were more commonly seen in females than in males. This difference is not statistically significant.

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Table 3: Severity of Dengue and Mucocutaneous Manifestations

	No of Dengue Fever Cases	No of Dengue Cases with Mucocutaneous Manifestations	Percentage with Mucocutaneous Manifestation
Dengue Without Warning Signs	174	114	65.52%
Dengue with Warning Signs	75	55	73.33%
Severe Dengue	47	42	89.36%
Total	296	211	

Dengue fever was classified based on WHO guidelines 2012 into three categories, Dengue Fever without warning sign, Dengue Fever with warning sign and Severe Dengue. Out of 174 cases of Dengue Fever without warning Signs, 114 cases developed mucocutaneous manifestations i.e. 65.52%. Out of 89 cases of Dengue Fever with warning signs, 55 developed Mucocutaneous Manifestation ie 73.33% and out of 47 cases in Severe Dengue group, 42 cases developed Mucocutaneous Manifestations i.e. 89.36%. Mucoccutaneous Manifestations were more commonly seen in Severe Dengue compared to Dengue fever with warning signs and Dengue fever without warning signs which was statistically significant (p value < 0.05).

Discussion

All the Mucosal Manifestations of Dengue Fever were further analyzed statistically for range of occurance, mode in days and average no of days of occurrence with mean and standard deviation.There were more males than females diagnosed with dengue fever. The ratio of M: F being 1.19:1.Slight increase preponderance of males in all the above studies could be because of reference bias.

In our study, mucocutaneous manifestations were observed more commonly in females with dengue fever (79.34%) than in males with dengue fever (65.71%) but this difference was not statistically significant.In our study, highest number of cases of children with dengue fever were in the age group of 6-10 years followed by in the age group of 11-15 years. Mucocutaneous manifestations were seen more commonly in age group of 16-18years. Other studies have not compared incidence of mucocutaneous manifestations in different age groups.

In present study, dengue cases were classified according to severity into three groups namely, Dengue Fever without Warning Signs, Dengue Fever with Warning Signs, and Severe Dengue according to the WHO 2012 protocol. There were 174 cases of Dengue Fever without warning Signs, 75 cases of Dengue fever with warning signs, and 47 cases of Severe Dengue.

Other studies have classified dengue in Dengue fever, Dengue haemorrhagic fever and Dengue shock syndrome according to WHO 1997 protocol which was followed till 2009.DHF was seen in around 9 -18 % and DSS in around 2.4 to 10.42% in dengue patients in various studies. Slightly increase in incidence of dengue fever with warning signs and severe dengue (equivalent of previous DHF and DSS) could be because of change in the epidemiology over the years. Incidence of mucocutaneous manifestations were 65.52%, 73.33% and 89.36% in Dengue fever without warning sign, Dengue fever with warning signs and Severe Dengue respectively. Mucocutaneous manifestations were more commonly seen in severe dengue than in other two groups, this was statistically significant (p value < 0.05).

Study by Thomas EA et al found haemorrhagic manifestations on the skin such as petechiae, purpura, or ecchymosis with positive tourniquet test, more commonly in DHF and DSS than in DF and also mucosal involvement more commonly in patients with DHF than with DF.[7]

The spectrum of dengue varies from asymptomatic infection to death. Cutaneous findings are prominently seen in patients of dengue fever. In present study, 79% of dengue patients had mucocutaneous manifestations. In our study, we studied the incidence of mucocutaneous manifestations in children with dengue fever, spectrum of mucocutaneous manifestations, their day of occurrence, and relation of severity of dengue and mucocutaneous manifestations. There are a very few studies on mucocutaneous manifestations of dengue fever, but not a single published study exclusively in children. Mucocutaneous manifestations are commonly seen in Dengue fever. In our study, 79.57% children with dengue fever had mucocutaneous manifestations, which is similar to Mahboob A et.al study[8] with incidence of mucocutaneous manifestations of 80% among patients between age group of 5 -68 years. Incidence of mucocutaneous manifestations in dengue fever was found to be 68% and 65% in studies done by Saleem K et al[9] from Karachi and Nadia AA et al.[10] from Lahore respectively.

Conclusion

- Mucocutaneous manifestations are commonly seen in children with dengue fever with incidence of 71.28% in our study.
- No significant difference in incidence of mucocutaneous manifestations is found in our study in males and females, and in different age groups.
- Although mucocutaneous manifestations are seen across all severity of Dengue fever but are more commonly associated with severe dengue.

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