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Diagnostic Profile of Dengue Fever - A Retrospective Report.

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Abstract: *Dengue is almost endemic all over India. Confirmation of Dengue viral infection is the most important and essential pre-requisite for the managing complications associated with Dengue viral infection. Infection with any of the DENV serotypes may be asymptomatic in the majority of cases or may result in a wide spectrum of clinical symptoms (2), ranging from a mild flu-like syndrome (known as dengue fever [DF]) to the most severe forms of the disease, which are characterized by coagulopathy, increased vascular fragility, and permeability. Efficient and accurate diagnosis of dengue is of primary importance for clinical care (i.e. early detection of severe cases, case confirmation and differential diagnosis with other infectious diseases), surveillance activities, outbreak control, pathogenesis, academic research, vaccine development, and clinical trials. Laboratory diagnosis methods for confirming dengue virus infection may involve detection of the virus, viral nucleic acid, antigens or antibodies, or a combination of these techniques. Present study has been done to know the sero prevalence of dengue viral infection among adults in a tertiary care health center. An attempt was made for correlating clinical manifestations along withdiagnostic parameters of dengue viral infection. Cross sectional evaluation was conducted during 2015-2017 at a tertiary care centre . Patients admitted with acute febrile disorder, clinically diagnosed as having dengue viral fever as per to the WHO criteria are included in the study and results were analysed.Our results suggest that a combination of clinical picture, hematological parameters (thrombocytopenia), and presence of IgM antibodies could be used as supportive markers for the early diagnosis of dengue infection.*

Keywords: *Dengue Virus, Diagnostic Profile*

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I. Inroduction

Dengue virus (DENV) belongs to the family Flaviviridae, genus Flavivirus, and is transmitted to humans by Aedes mosquitoes, mainly Aedes aegypti. Based on neutralization assay data, four serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) can be distinguished. DENV infection is a major cause of disease in tropical and subtropical areas, with an estimated 50 million infections occurring each year and more than 2.5 billion people being at risk of infection (1). Dengue is almost endemic all over India. Confirmation of Dengue viral infection is the most important and essential pre-requisite for the managing complications associated with Dengue viral infection. Infection with any of the DENV serotypes may be asymptomatic in the majority of cases or may result in a wide spectrum of clinical symptoms (2), ranging from a mild flu-like syndrome (known as dengue fever [DF]) to the most severe forms of the disease, which are characterized by coagulopathy, increased vascular fragility, and permeability (dengue hemorrhagic fever [DHF]). The latter may progress to hypovolemic shock (dengue shock syndrome [DSS]). In Asia the risk of developing severe disease is greater in DENV-infected children (≤15 years) than in adults (3,4)Efficient and accurate diagnosis of dengue is of primary importance for clinical care (i.e. early detection of severe cases, case confirmation and differential diagnosis with other infectious diseases), surveillance activities, outbreak control, pathogenesis, academic research, vaccine development, and clinical trials.Laboratory diagnosis methods for confirming dengue virus infection may involve detection of the virus, viral nucleic acid, antigens or antibodies, or a combination of these techniques. After the onset of illness, the virus can be detected in serum, plasma, circulating blood cells and other tissues for 4–5 days. During the early stages of the disease, virus isolation, nucleic acid or antigen detection can be used to diagnose the infection. At the end of the acute phase of infection, serology is the method of choice for diagnosis.

Antibody response to infection differs according to the immune status of the host (5). When dengue infection occurs in persons who have not previously been infected with a flavivirus or immunized with a flavivirus vaccine (e.g. for yellow fever, Japanese encephalitis, tick-borne encephalitis), the patients develop a primary antibody response characterized by a slow increase of specific antibodies. IgM antibodies are the first immunoglobulin isotype to appear. These antibodies are detectable in 50% of patients by days 3-5 after onset of

illness, increasing to 80% by day 5 and 99% by day 10 . IgM levels peak about two weeks after the onset of symptoms and then decline generally to undetectable levels over 2–3 months. Anti-dengue serum IgG is generally detectable at low titres at the end of the first week of illness, increasing slowly thereafter, with serum IgG still detectable after several months, and probably even for life (6-8).A range of laboratory diagnostic methods has been developed to support patient management and disease control. The choice of diagnostic method depends on the purpose for which the testing is done (e.g. clinical diagnosis, epidemiological survey, vaccine development), the type of laboratory facilities and technical expertise available, costs, and the time of sample collection.Current diagnostic methods used are 1) viral culture 2) viral RNA detection by reverse transcriptase polymerase chain reaction(RT- PCR) and 3) serological tests. Detection of IgM immunoglobulin and NS 1 antigen are routine serological tests used for diagnosis of acute Dengue viral infection (Datta et al., 2010).Dengue NS1 antigen identification is possible as early as day one of onset of fever, as it appears in serum in initial phase of infection. Dengue IgM immunoglobulin usually starts appearing in serum 2-5 days after the infection. Hence pooling both results of Dengue IgM antibody and NS1 antigen gives a more accurate diagnosis in acute phase. Apart from specific markers of Dengue virus, platelet count is the sole supportive test which is in reach of many laboratories mainly in peripheral areas. (9)

Present study has been done to know the sero prevalence of dengue viral infection among adults in a tertiary care health center. An attempt was made for correlating clinical manifestations along withdiagnostic parameters of dengue viral infection.

II. Methodology

Cross sectional evaluation was conducted during 2015-2017 at a tertiary care centre .Patients admitted with acute febrile disorder, clinically diagnosed as having dengue viralfever as per to the WHO criteria are included in the study. Patients with history of prolonged fever of more than one month and patients with any other proven febrile illnesses like Malaria, Typhoid etc. are excluded from the study. Hb%., total count, differential count, peripheral smear, platelet count and hematocrit values of these patients along with serum IgM antibody detection and ImmunoChromatographic Test (ICT) were documented . NS1 antigen was identified by using ICT.

III. Results

The study included 143 patients with clinically suspected DEN viral infection. A male preponderance (61%) was noted. A total of 23 (54%) patients were in the age group of 21–40 years, followed by 8 (19%) patients who were 20 years or below, 6 (14%) in the age group of 41–50 years and 5 (12%) patients were above 50 years. Fever was the most common presenting symptom. 68 (48.8%) patients had a history of ≤5 days of fever, while 73 (51.2%) reported after >5 days of fever. Haematological investigations revealed thrombocytopaenia in 30 (72%) cases. comorbid conditions such as malignancy, diabetes mellitus and ischaemic heart disease were seen in eight patients and one patient succumbed to the illness.out of 143 suspected cases, 42 (29%) cases were positive by at least one of the following tests-igm elisa, iggelisa, ns1 elisa; 28 (65%) patients with a history of ≤5 days of fever and 14 (35%) patients with a history of >5 days fever. secondary infection (igm-to-igg ratio <1.2) was observed in 9 of the 42 cases.of the 42 samples positive for ns1 antigen and/or igm/igg antibodies, 36 samples were processed by real-time rt-pcr for detection of viral rna, while the rest (6 samples) could not be processed due to insufficient quantity. of the 101 cases negative for den by ns1 antigen and/or igm/igg antibodies, 42 cases had a history of <5 days of fever at presentation. out of these 42 samples, 24 samples were further processed by real-time rt-pcr for detection of viral rna, 5 samples had insufficient quantity and rest of the 13 cases were excluded because another infectious aetiological agent was identified in these samples. therefore, a total of 60 samples were processed for detection of viral rna and serotyping by multiplex real-time rt-pcr. 18/60 (29%) samples were positive for den viral rna and the serotypes identified were denv 1, 2 and 3. pcr was positive in 13 of 17 (79%) cases with a history of ≤5 days of fever positive by igm/igg elisa (significant, $p = 0.033$) and in 14 of 17 (89%) cases positive by ns1 elisa (significant, $p = 0.010$). however, pcr was positive in only 1 of the 24 cases with a history of ≤5 days, negative by ns1/igm/igg elisa.

IV. Discussion

DENV is an emerging vector-borne disease. Rapid urbanisation, globalisation, poor solid waste and water management and increasing population have given rise to new habitats for mosquito breeding thereby increasing the number of cases.Majority of our cases (40%) were detected exclusively by the presence of viral NS1 antigen compared to IgM (7%) antibodies in patient's sera. It is known that early detection of DEN cases by NS1 assay helps in diagnostic detection and confirmation of cases (10,11). NS1 antigen detection is particularly useful during the first 5 days of illness and significantly more sensitive for primary than secondary DEN infection as was also seen in our study (12-14). Five percent of NS1-positive samples were also IgG positive. These patients provided serological evidence of previous exposure. It is a known fact that during a primary

infection, individuals develop IgM after 5–6 days and IgG antibodies after 7–10 days.Majority of the patients (71%) presenting with fever of >5 days in our study were positive for IgM ELISA as compared to other serological parameters. In 2007, Kumarasamy et al. compared the use of NS1 ELISA with viral isolation in cell cultures and RT-PCR assay and achieved great results in patients in the early stages of infection concluding that NS1 antigen detection may be an appropriate marker of acute DENV infection (15)

V. Conclusion

These results suggest that a combination of clinical picture, hematological parameters (thrombocytopenia), and presence of IgM antibodies could be used as supportive markers for the early diagnosis of dengue infection.NS1 antigen detection was found to have a better sensitivity than viral RNA detection by PCR for early detection of DEN infection. NS1 antigen when combined with IgM capture ELISA increased the diagnostic efficacy. Periodic monitoring of circulating DEN viral serotypes is essential for epidemiological purposes and for the patient management.

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