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PROFILE OF SEROLOGICAL, HAEMATOLOGICAL AND BIOCHEMICAL DYNAMICS IN DENGUE FEVER

Biochemistry

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ABSTRACT

Aim: The objective of this study is to determine serological, haematological and biochemical dynamics to use results to predicts the severity of dengue fever and early treatment of affected patients.

Method: A total number of 308 patients with clinical and serological diagnosis of fever were admitted in Shadan Institute of Medical Sciences,Teaching Hospital and Research Center, Hyderabad, Telangana, India.The patients were allotted to two groups according to age under 15 years old (n = 132) and 15 years or older (n = 176). The serological, haematological and biochemical parameters were analysed. Dengue is caused by one of the four serotypes of the dengue virus (DEN-1, DEN-2, DEN-3, and DEN-4). Also referred to as an arbovirus (arthropod - borne virus) that belongs to the genus Flavivirus of the family Flavivirdae. 1-3. The tests analysed were serological immunoglobulins(IgG, IgM, IgA & NS1) blood count, platelets count, serum total proteins, total bilirubin,aminotransferases, alkaline phosphatase, gamma glutamyl transferase, lactate dehydrogenase concentrations and the duration of prothrombin and activated partial prothrombin time.

Results: Elisa IgG, IgM, IgA antibodies against dengue virus and NS1 dengue antigen in human by captured method are found positive for Dengue Virus. The blood count, platelets count, serum total proteins, total bilirubin, aminotransferases, alkaline phosphatase, gammaglutamyl transferase, lactate dehydrogenase concentrations and the duration of prothrombin and activated partial prothrombin time were found elevated .

Conclusion: These results are relevant in assessing the disease because they can be used as positive markers for more severe forms and can help by enabling the adaption of the conduct to the need of individual patients.

KEYWORDS

Dengue fever, dengue virus, prognosis, Immunoglobulins, NS1, blood count, platelets count, serum total proteins, total bilirubin, aminotransferases, alkaline phosphatase, gamma glutamyl transferase, lactate dehydrogenase concentrations and the duration of prothrombin and activated partial prothrombin time.

INTRODUCTION:

Dengue is caused by one of the four serotypes of the dengue virus (DEN-1, DEN-2, DEN-3 and DEN-4) also referred to as an Arbovirus (arthropod-borne viruses) that belongs to the genus Flavivirus of the family Flaviviridae [1,2]. It is a disease with a wide clinical spectrum and a wide variety of presentations, ranging from asymptomatic to an undifferentiated fever (viral syndrome) to the more severe forms such as severe dengue (SD) or Dengue Hemorrhagic Fever (DHF)[3]. Transmission to humans occurs by the bite of the female Aedes aegypti mosquito infected by one of four serotypes of the virus. This mosquito is a domestic species adapted to urban conditions[4].

The period of transmission from humans to mosquitoes begins one day before the starting of fever up to the sixth day of illness corresponding to the viremia phase. After a female bites an individual in the viremia phase, viral replication (extrinsic incubation) begins in the vector from eight to twelve days. In humans, the incubation period ranges from 3 to 15 days (intrinsic incubation) with an average of 5 days [4-8]. The diagnosis of dengue fever is carried out based on clinical, epidemiological and laboratory data. Among laboratory tests, both non-specific [blood count, platelet count, tourniquet test, prothrombin time (PT), activated partial thromboplastin time (APTT), liver function tests and serum albumin concentration] and specific tests (viral isolation tests and serology for antibody and antigen examination) are used [9, 10].Leukopenia is the most prominent haematological change, sometimes with counts of less than 2x103/µL. However, there are reports of mild leukocytosis at the onset of the disease, with neutrophilia. Lymphocytosis is a common finding, with the presence of atypical lymphocytes. The hematocrit concentration should be monitored according to the days of illness, remembering that, with the progression to DHF, there will be a 20% increase in hematocrit from the patient's baseline, associated with thrombocytopenia (< 100 x 109/L)[11,12]. The biochemical variables, the most frequent changes occur in liver function tests such as in serum total protiens, total bilirubin, serum aspartate aminotransferase(AST), serum alanine aminotransferase(ALT), alkaline phosphatase, Gamma-glutamyl transpeptidase and lactate dehydrogenase levels[9]. The present study aimed to assess the serological, biochemical and haematological dynamics of patients with dengue fever in order to increase the sensitivity of the screening by healthcare professionals in the most serious cases and try to identify laboratory markers that may indicate this evolution. The results are relevant in assessing the disease because they can be used as positive markers for more severe forms and can help by enabling the adaption of the conduct to the need of individual patients

METHODS:

This is a descriptive observational retrospective study of secondary data obtained from the medical records of 308 male and female patients aged from 2 to 85 years who had serological diagnoses of dengue fever in Shadan Institute of Medical Sciences,Teaching Hospital and Research Center, Hyderabad, Telangana, India.. The patients were allotted to two groups that is a referral centre for infectious and contagious diseases. The study included all patients diagnosed with positive serology for dengue using ELISA serological immunoglobulins (IgG, IgM, IgA & NS1) by capture method. Beside these haematological parameters such Heamoglobin, Heamatocrit, Total Lecocyte count, lymphocytes and thrombocytes were analyse by cell counter Medonic and biochemical parameters such as serum total proteins, total bilirubin, serum aspartate aminotransferase(AST), serum alanine aminotransferase(ALT), alkaline phosphatase, Gamma-glutamyl transpeptidase and lactate dehydrogenase levels[9] done by Cobas 311 C. PT And APTT were done by Tulip method all these parameters are found very much significant in dengue fever.

Some clinical presentations of dengue fever and laboratory findings are different in adults compared to children so the study population was divided into two groups (Table 1): under 15-year-

old patients and those aged 15 years old or more.

Table 1: Patients and the clinical classification of dengue:

Type n(%)	Age < 15 years	Age ≥ 15 years	Total n(%)
Classic dengue fever	13 (2.60)	37(10.39)	50
Severe dengue fever	36(11.69)	52 (16.88)	88
Dengue hemorrhagic fever	92 (29.87)	78 (28.57)	170
Total	50(42.86)	88(57.14)	170 (65.95)

Mean SD + p value = 0.06

The difference in the proportion of clinical forms of dengue fever between under 15-year-old patients and older patients

Table 2:
Patients grouped by gender and the clinical classification of dengue:

Type n(%)	Female	Male	Total n (%)
Classic dengue fever	20 (06.50)	20 (06.50)	40
Severe dengue*	61 (18.83)	37 (09.74)	98
Dengue hemorrhagic fever	86 (27.92)	94 (30.51)	170
Total	40 (33.52)	98(46.51)	170 (68.82)

PATIENTS AND THE CLINICAL CLASSIFICATION OF DENGUE:

Patients were classified into classic dengue fever (CD), dengue hemorrhagic fever (DHF). Mean SD (3,14) The first day of the disease was considered the onset of symptoms related to dengue fever and the laboratory profile was evaluated for the first 12 days. The variables selected were: hemoglobin (Hb), hematocrit (Ht), leukocytes, lymphocytes, blood count, platelets count, serum total protiens, total bilirubin, aminotransferases, alkaline phosphatase, gamma glutamyl transferase, lactate dehydrogenase concentrations and the duration of prothrombin and activated partial prothrombin time.

RESULTS:

The results of 308 patients with clinical and laboratory dengue fever were analyzed; female 82 (53.25%) and male 72 (46.75%) (Table 2). The ages ranged from 2 to 85 years with 33.7% aged from 0 to 9 years (Figure 1). Regarding the clinical form of the disease, 20 (13%) had CD, 44 (28.6%) had SD and 90 (58.4%) had DHF. There was a predominance of women with SD (p-value = 0.01).

FIGURE 1: Distribution of study population according to age (n = 308).

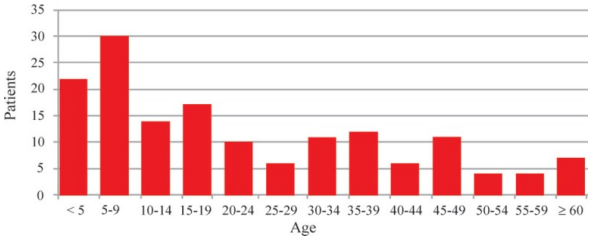
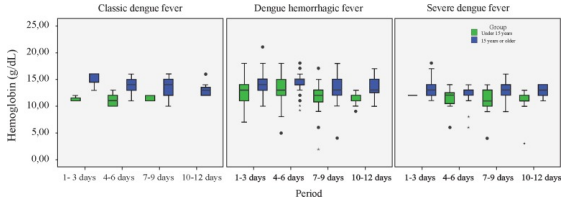


FIGURE 2:
Dynamics of hemoglobin levels in patients with dengue fever according to age group (< 15 years and ≥ 15 years) and clinical form.



In relation to the values of Hb, we found that for the group aged 15 years or over with CD, there was a greater variation in the course of the disease; however, there were no significant differences between groups. For DHF we observed a greater variation of Hb in both groups which was most evident from the 4th to 6th days with the highest values in the group of patients aged 15 years old or more. For SD, there is a slight variation between the groups (Figure 2).

FIGURE 3:
Dynamics of hematocrit levels, we found homogeneous and lower values in the under 15-year-old age group for all forms but with a greater variation in DHF .

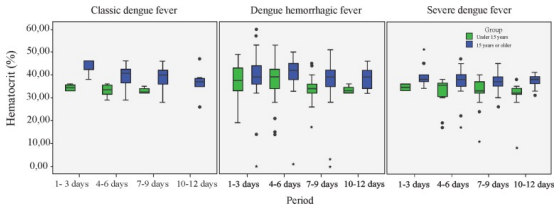
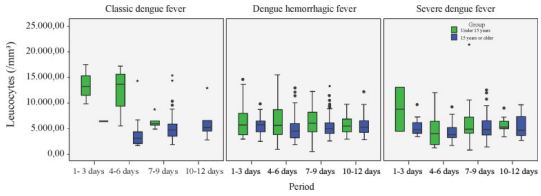
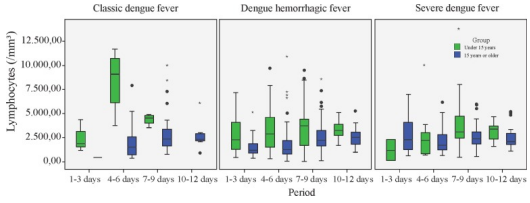


FIGURE 4:
Dynamics of the absolute number of lymphocytes in patients with dengue fever according to age group (< 15 years and ≥ 15 years) and clinical form.



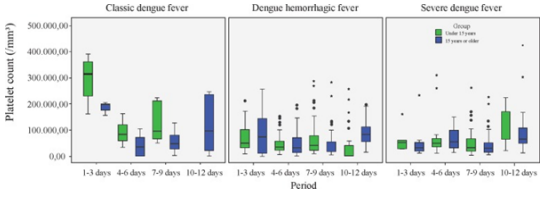
Leukocytosis was observed in patients with the CD in the first days of the disease, followed by leukopenia, which was more pronounced in the under 15-year-old age group.For the other forms of the disease, the values were similar throughout the evolution (Figure 4).

FIGURE 5:
Dynamics of the absolute number of lymphocytes in patients with dengue fever according to age group (< 15 years and ≥ 15 years) and clinical form.



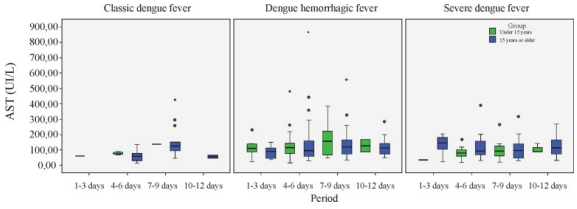
Lymphocytosis was observed in all forms, especially in the under 15-year-old age group, during the course of the disease, but this was more pronounced in CD from the 4th to 6th days (Figure 5).

FIGURE 6:
Dynamics of platelet count in patients with dengue fever according to age group (< 15 years and ≥ 15 years) and clinical form



In CD, thrombocytopenia was observed in both age groups from the 4th day of the disease. The DHF and SD forms started with thrombocytopenia and pronounced variations were recorded throughout the evolution in both age groups (Figure 6).

FIGURE 7:
Dynamics of serum aspartate aminotransferase in patients with dengue fever according to age group (< 15 years and ≥ 15 years) and clinical form



Increases in the AST enzyme occurred at the beginning of the disease and remained stable for all clinical forms; this was more pronounced in the under 15-year-old age group. Increases in ALT were detected from the 7th day in CD and DHF, which remained high throughout the course of the disease mainly in the under 15-year-old age group. In SD the increase in ALT was recorded at onset in under 15-year-old patients (Figure 7)

FIGURE 8:
Dynamics of serum alanine aminotransferase in patients with dengue fever according to age group (< 15 years and ≥ 15 years) and clinical form

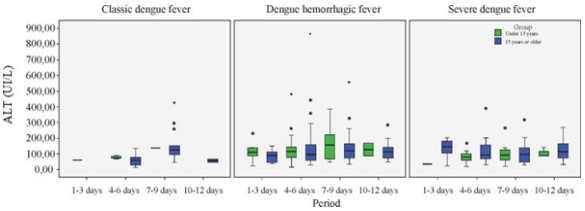


FIGURE 9:
Dynamics of serum alkaline phosphatase in patients with dengue fever according to age group (< 15 years and ≥ 15 years) and clinical form.

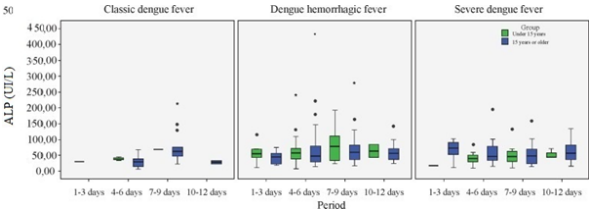


FIGURE 10:
Dynamics of serum alkaline phosphatase in patients with dengue fever according to age group (< 15 years and ≥ 15 years) and clinical form.

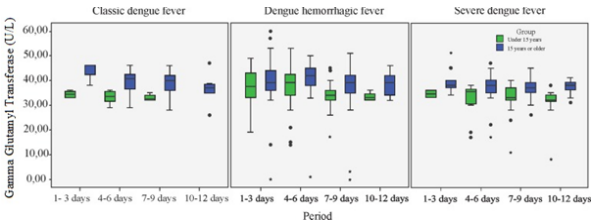


FIGURE 11:
Dynamics of serum Lactate dehydrogenase in patients with dengue fever according to age group (< 15 years and ≥ 15 years) and clinical form.

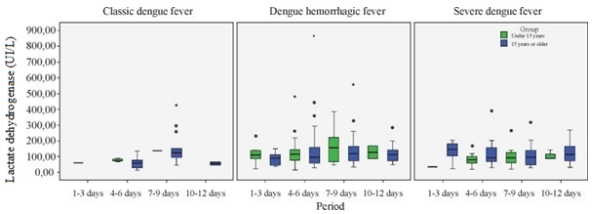


FIGURE 12:
Dynamics of prothrombin time in patients with dengue fever according to age group (< 15 years and ≥ 15 years) and clinical form.

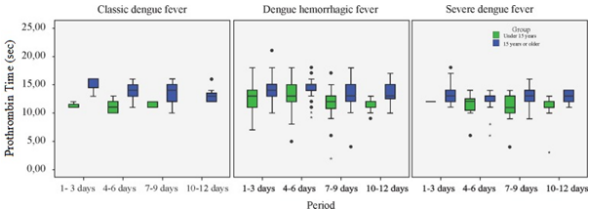
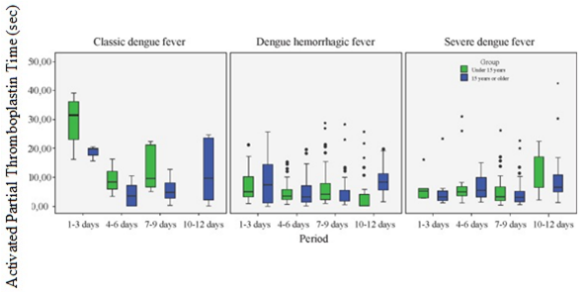


FIGURE 13:
Dynamics of activated partial thromboplastin time in patients with dengue fever according to age group (< 15 years and ≥ 15 years) and clinical form.



DISCUSSION:
Dengue fever is an infectious disease which is difficult to distinguish from other viruses prevalent in our region as there are no specific markers that can diagnose the disease early. Because it is a disease that can evolve with serious consequences and even be fatal, this study aimed at analyzing clinical and epidemiological data and laboratory dynamics in order to try to identify biomarkers that are predictive of severity. In our study, the worst clinical forms, DHF and SD, were prevalent possibly because the patients were admitted in a tertiary hospital specialized in infectious diseases. Oliveira et al., [15] in a study on outpatients, showed a predominance of the classical form of the disease.

The frequency of dengue fever in the study was higher in the group aged 15 years old or over. These results are similar to those of Rocha &Tauil[16] in an epidemiological study conducted in Manaus, AM. There was a slight predominance of women in this study; in most published studies, there is no significant difference in the proportions by gender.[16] The correlation between gender and the clinical form showed a significant difference for SD, with a predominance of women, a result that is in disagreement with the literature.[12,13]

Regarding the clinical forms of dengue, only DHF showed peak elevations in Hb and Ht during the course of the disease, a change most likely attributed to hemoconcentration, which can lead to hypovolemic shock.[4,5,17]

It was found that CD began with leukocytosis and leukopenia appearing later. Leukopenia was more pronounced in the CD and DHF clinical forms and in patients of 15 years old or older, similar to other published results.[13] There was a decrease in lymphocytes at the onset of dengue fever, with an increase as the disease progressed; this was statistically significant in all three clinical forms for under 15-year-old patients.

In the hemorrhagic and severe forms, thrombocytopenia occurred from the onset of symptoms and remained stable throughout the progression of the disease. This was more evident in the older age group. In CD, thrombocytopenia started late. This result is in agreement with the literature, which reports moderate or severe thrombocytopenia in DHF.[11,12,15] The inflammatory responses to dengue are attributed to immune complex formation, complement activation and the release of cytokines into the circulation in a phase prior to the most serious forms of the disease. The mechanisms underlying the bleeding in DHF are multiple including vasculopathy, thrombopathies and DIC. Thrombopathy consists of thrombo cytopenia and platelet dysfunction.[18]

AST levels increased at the onset of symptoms in all clinical forms and remained at varying but high levels during disease evolution; this was particularly prominent in under15-year-old patients. ALT started with above normal values in the severe form and remained steady throughout the course of the disease; in the classic and hemorrhagic forms, the increases occurred progressively.

Similar results were obtained by Chen et al.,[19] who showed that both AST and ALT exhibited higher-thanaverage values in under 15-year-old patients with DHF. Chau et al.[20] found a significant increase in transaminases, especially AST, in children with dengue when compared to a control group with other febrile (non-dengue) illnesses.

For Chacko & Subramanian,[21] an increase in ALT (≥ 40 IU) in children with dengue fever can be considered a predictive marker for shock

syndrome. The liver is one of the target organs for dengue and clinical manifestations of hepatic dysfunction can occur during the course of this disease.[22] The liver is deprived of oxygen leading to lesions of the parenchyma, in which the injured hepatocytes release transaminases that is detectable in the peripheral blood.[23] In most cases, the high levels of transaminases show the degree of hepatocellular injury, prolonging the clinical course of the disease; however, there is no correlation with prognosis.[24-26]

CONCLUSION:

Dengue fever evolves with laboratory alterations starting on the 3rd day and becoming most evident on the 5th day with values restored to normal by the 11th day. The disease was more severe in individuals aged 15 years and older with a more pronounced and persistent presence of liver abnormalities (AST, ALT) and hem concentration. The study results are relevant in the characterization of biological markers in the evolution of the disease and can be used as markers for the most severe forms thereby enabling early help with the adaption of therapeutic conduct for specific patients.

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