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EARLY HEMATOLOGICAL PARAMETERS AS PREDICTORS FOR OUTCOMES IN CHILDREN WITH DENGUE IN SOUTHERN INDIA: A RETROSPECTIVE ANALYSIS

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ABSTRACT:

Introduction: Dengue presents with a variable clinical course, ranging from mild illness to potentially fatal hemorrhage and shock. We aimed to evaluate the capabilities of various hematological parameters observed early in the course of illness for predicting the clinical outcomes of illness.

Material and Method: In our study total 100 cases aged from 0 to 18 years who had diagnosed to have dengue fever were taken. The presenting clinical features were collected and analyzed. The laboratory results analyzed were blood count including Hemoglobin level, hematocrit level, leucocyte count and platelet count.

Results: In the present study, 29/100 (29.0%) cases were of dengue without warning sign, 49/100 (49.0%) were dengue with warning signs and 22/100 (22.0%) were of severe dengue. Patient age ranged from 0- 18 years. Majority, 52/100 (52.0%) were among 6-8 years. Males were affected more than females (55% boys and 45% were girls). Severe thrombocytopenia was seen in 57.0 % of cases and raised hematocrit (>47%) was observed in 22.0 % cases. Most of the cases 65 (65.0%) were noted in August and September.

Conclusion: We identified important clinical presentations and useful hematological parameters to enable the early prediction for outcome in children with dengue. An accurate diagnosis using these data will enable further investigation to be tailored and early treatment for the patient.

Keywords: Hemorrhagic fever. Leucocyte count. Mean platelet volume. Platelet count. Dengue fever in children, Platelet count, Thrombocytopenia, NS1Ag, Complete blood count, Hematological parameters

INTRODUCTION

For the last three decades, dengue has continued to pose a major public health problem worldwide. Globally, there are approximately 100 million infections reported each year with up to 2% resulting in a fatal outcome. [1] These outbreaks persistently challenge regional health systems and the economy, particularly in developing countries where they are more prevalent. The economic impact of dengue in India in 2006 was estimated to be USD 27 million. [2]

Dengue targets people from a wide range of sociodemographic characteristics and contributes to considerable morbidity and mortality in the pediatric population. [3] It presents with a spectrum of clinical courses among children, ranging from minor insignificant illness to potentially fatal hemorrhage and shock. Globally, researchers are striving to unearth the determinants of its anticipated clinical course to utilize the available resources with maximum cost effectivity. The proposed determinants range from certain clinical features [4] along with common laboratory parameters [5] to specific biomarkers and gene expression and have variable clinical applicability. Among the hematological parameters, hemoconcentration and thrombocytopenia markers are the most widely studied and utilized for clinical decisions. [6]

As hematological derangements are among the most frequently observed manifestations in severe dengue infection, we theorized that detailed exploration of hematological parameters, including red cell indices and platelet size, observed early in the course of illness might predict various clinical outcomes. Being commonly available and routinely performed as part of investigations, these predictive factors could assist clinicians in resource-limited settings to identify children with anticipated severe illness.

Material and Methods

This was a descriptive retrospective study conducted in paediatric department sree mookambika institute of medical sciences. Total 100 dengue cases of age group 0-18 years were taken. They were diagnosed to have DF if they had positive serology result for dengue using the ELISA IgM and/or ELISA NS1. Any child with fever, but seronegative for DF, were excluded from the study.

The exclusion criteria included children proved to have malaria, cancer, tuberculosis, HIV, and bacterial and parasitic illnesses, and those who were on any medications (antibiotics, antipyretics, anti-inflammatory) for the past 2 months. Our patients were diagnosed according to revised WHO classification criteria as Dengue without Warning Signs, Dengue with Warning Signs (abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver enlargement, increasing hematocrit with decreasing platelets) and Severe Dengue (SD). [7]

The criteria were designed to classify cases of severe dengue into three specific subcategories: severe vascular leakage, severe bleeding, and severe organ dysfunction. These criteria could allow clinicians to evaluate progression of disease or pathogenesis in a more focused way, allowing new fields of scientific research. [8]

Hematological investigation data including complete blood counts using fully automated hematology analyzer and peripheral smear stained with Leishman stain were collected from all patient records or files. Moreover, serological investigation data were taken in such patients.

Hemoconcentration was seen as raised hemoglobin (Hb) or red blood corpuscles count. Leukopenia was considered if white blood cell (WBC) count was less than $4000\times10^3/\mu l$ and thrombocytopenia was less than $150\times10^3/\mu l$. The data of our patients fulfilling mentioned inclusion and exclusion criteria were collected and entered into the Microsoft Excel (Microsoft Corp., Redmond, WA, USA). All demographic data and clinical manifestations were categorized into frequency, whereas mean ± SD for laboratory results.

Result

A total of 100 children were included in the present study. In the present study, 39/100 (39.0%) cases were of dengue without warning sign, 49/100 (49.0%) were dengue with warning signs and 22/100 (22.0%) were of severe dengue.

Table-1: Age-wise distribution of cases.

Age	No. of cases	Percent (%)
0-2 years	04	4.0%
3-5 years	13	13.0%
6-8 years	52	52.0%
9-11 years	20	20.0%
12-14 years	6	6.0%
15-18years	5	5.0%
Total	100	100%

In the present study, age group distribution included from 0 to18 years. Majority of the cases were among 6-8 years age.

Gender-wise distribution of cases: in the present study, there were 55 (55%) boys and 45 (45%) girls and the male to female ratio was 1.4:1.

Table-2: Clinical symptoms of the cases.

Clinical Symptoms	No. of cases	Percent (%)
Fever	100	100%
Myalgia	80	80.0%
Fever and myalgia	85	85.0%
Fever with rash	35	35%
Petechiae	18	18.0%
Abdominal pain	40	40.0%
Nausea and vomiting	60	60.0%
Ascites	08	8.0%
Shock	04	4%

In the present study, fever was present in all 100% of the cases.

Table-3: Hemoglobin range.

Hb	No. of cases	Percent (%)
< 5gm%	03	3.0%
5-10 gm%	31	31.0%
10-15 gm%	62	62.0%
>15 gm%	04	4.0%
Total	**100**	**100%**

Present study showed hemoglobin range from less than 5 gm% to more than 15 gm%. Almost half (52.0%) cases showed hemoglobin value between 10-1 5 gm%.

Table-4: Hematocrit value.

Hematocrit	No. of cases	Percent (%)
26-36%	03	3.0%
37-47%	75	75.0%
>47%	22	22.0%
Total	**100**	**100%**

Raised hematocrit (>47%) was observed in 22.0% cases (22/100).

Table-5: Total leukocyte count and platelet count.

TLC/ cumm	No. of cases	Percent (%)	Platelet count/cumm	No. of cases	Percent (%)
< 4000	17	17.0%			
			<50000	57	57.0%
4000-11000	80	80.0%	50000- 1.0 lakhs	31	31.0%
>11000	03	3.0%	1.0-1.5 lakhs	12	12.0%
Total	**100**	**100%**	**Total**	**100**	**100%**

Total WBC count was within normal limits (4000-11000/cumm) in 80.0% cases. Moderate thrombocytopenia (50000-1.0 lakh/cumm), was seen in 31.0% (31/100) and severe thrombocytopenia was seen in 57.0% (57/100) cases.

Liver enzymes were elevated in 65 (65.0%) cases and were normal in 35 (35.0%) cases.

USG findings: Ultrasound of the abdomen showed hepatomegaly in 62 (62.0%) of the cases, ascites in 14% and pleural effusion in 15% cases.

NS1 Ag: NS 1 antigen test was positive in 85% of cases, serum dengue IgM in 55% and dengue IgG was positive in 42% of cases.

Seasonal Variation: Most of the cases 65 (65.0%) were noted in August and September months and 30 (30.0%) cases were recorded in July and October.

Discussion

Dengue is a major public health problem in tropical and subtropical areas worldwide. There is a lack of information on the risk factors for death due to severe dengue fever in developing countries. [9] It is a viral infection with fatal potential complications. It is also called as break bone fever. Worldwide dengue infection is the most common mosquito borne viral disease. [10]

In our study, the dengue cases had higher hemoglobin levels and a higher hematocrit from day 3 to day 10 (highest on day 7), lower white blood cell (WBC) count from day 2 to day 10 (lowest on day 5) and lower plate-let count from day 3 to day 10 (lowest on day 6). The details of the differential WBC percentage were that the samples from the patients with dengue showed higher monocyte on day 1–4 (highest on day 2), higher atypical lymphocytes day 5–9 (highest on day 7) and higher eosinophils on day 9–10 (highest on day 9). Furthermore, the neutrophil to lymphocyte ratio in the dengue group was > 1 on the first 5 days then reversed on day 6 to day 9.

The dengue cases in our study, had higher hemoglobin levels and a higher hematocrit as a result of the plasma leakage. An in vitro study revealed a cross-reaction of pro-

inflammatory mediators such as tumor necrosis factor (TNF) - alpha and anti-NS1 antibodies with surface proteins on endothelial cells causing apoptosis of these cells and subsequently plasma leakage. [11]

The total white blood cell count was significantly lower in the dengue cases. Leukopenia occurred from day 2 and was lowest on day 5 of the fever. A hypothesis regarding the occurrence of the leukopenia in the cases of dengue infection was that it was caused by the destruction or inhibition of myeloid progenitor cells as the bone marrow examination showed mild hypo cellularity in the first seven days of fever then normal cellularity in the convalescent phase. [12]

Monocytosis occurred in 60–70% of patients in our study which was similar to previous study which found it in 84.6% of patients. [13] Another study showed that monocytosis was found in cases of dengue hemorrhagic fever more often than dengue fever. [14] Thus, monocytosis might be a parameter which can be used to predict the severity of dengue infection. A hypothesis as to why there is an increase in monocytes in the first few day of the fever is that monocytes and macrophages are the part of the primary immune which carry out phagocytosis of microorganisms and present the resulting carried antigen to the T helper cells. However, there were several conditions associated with monocytosis, for example other viral infections, enteric fever, malaria, tuberculosis, HIV, malignancy or pyrexia of unknown origin [15], so the monocytosis was not specific to dengue infection.

The neutrophils percentage was predominant in the first 5 days of the fever, a condition which was reversed, lymphocytes then predominating. This result was in agreement with a previous study which showed that lymphocytes predominated on day 10 of the fever. [16]

A study from Brazil and Pakistan had similar results to this study in terms of eosinophilia, the study showing that around 20% of patients had a higher eosinophil count on day 10 of the fever. [17] In cases of dengue infection, eosinophil levels were low in the acute phase due to the response to the inflammatory process, the levels then returning to baseline and increasing in the convalescence phase. [18]

Atypical lymphocytes increased on days 5–9 in the dengue cases in our study. The higher atypical lymphocyte percentage was found in cases of dengue hemorrhagic fever more than dengue fever. [19] Therefore the percentage of atypical lymphocytes may be another parameter useful in the pre-diction of the severity of dengue infection in addition to monocytosis. The study from India showed basophilic (basophil > 2%) in 52.9% of dengue patients. On the contrary to this result, the basophils were not elevated in our study. The cause of basophilic may be due to recovery from the bone marrow suppression in the convalescence phase. [20]

Half of the patients had thrombocytopenia on day 4 and increased up to 1.5 lakhs approximately 80% of cases on day 10. Although almost all patients had thrombocytopenia, but most of them were non-severe form of dengue infection so the bleeding diathesis of our

study was low (5.8%). There are several hypotheses to explain this such as an infected megakaryocyte by the virus, peripheral destruction and cross-reaction of antibodies against platelets. The platelets of dengue infected patients had mitochondrial dysfunction which activated the apoptosis cascade and led to cell death. Prolonged thrombocytopenia was found in dengue hemorrhagic fever more frequently than in cases of dengue fever, so the duration of thrombocytopenia is considered to be the predictor of the severity of dengue infection. Currently, the new parameter to reflect the rate of thrombopoiesis is the immature platelet fraction (IPF) which can be used to predict platelet recovery in dengue patients.

Cytopenia is the major parameter from the CBC which can distinguish dengue infection from the others. A review of a bone marrow study in dengue patients showed the transient suppression of hematopoiesis within 3–4 days of infection then the host inflammatory response which occurred to eliminate infected cells. Therefore, the cytopenia is probably a protective mechanism to limit injury to the marrow stem cells during the subsequent process of the eradication of infected cells. In addition, the dengue-infected endothelial cells are potentially bound to white blood cells, neutrophils, lymphocytes, platelets, and large lymphocytes in vitro but the monocytes, basophils, and eosinophils had no interaction. The increased binding of neutrophils and platelets to infected endothelial cells may explain neutropenia and thrombocytopenia in dengue patients. [21]

In addition to a previous study, our study included the changes in all CBC parameters on each successive day of the fever. The first parameter was monocytosis, followed by leukopenia, thrombocytopenia, a raised hematocrit, increased atypical lymphocytes and a reversed neutrophil to lymphocyte ratio respectively. The recovery phase started with the increase of white blood cell, hematocrit and platelet. We also found eosinophilia at this phase. [22]

Conclusion

We identified important clinical presentations and useful hematological parameters to enable the early prediction for outcome in children with dengue in south india population. An accurate diagnosis using these data will enable further investigation to be tailored and early treatment for the patient.

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CONFLICTS OF INTEREST:
There are no conflicts of interest

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