Clinicohematological profile of acute febrile illness: Experiences in a hospital catering to semi-urban pediatric population of Delhi

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ABSTRACT

Background: Among the pediatric age group, acute febrile illness (AFI) is a major cause of hospital admission, causing morbidity and death among children worldwide. Dengue, typhoid, malaria, and chikungunya fever are some of the common causes in Indian clinical settings. **Objective:** The objective of the study was to analyze the spectrum of AFI in pediatric population along with the evaluation of hematological parameters and to determine the specific causes and also the prognostic implications of these parameters. **Materials and Methods:** Patients from the pediatric outpatient department presenting with AFI formed the subjects of this study. Hematological profiles and biochemical investigations of atrial fibrillation cases were carried out and correlated. Statistical analysis was done. **Results:** In case of malaria and typhoid fever, leukopenia was statistically significant. Significant difference ($p<0.05$) was observed between severity of the thrombocytopenia and dengue fever and malaria. **Conclusion:** The study focuses the importance of clinical and hematological parameters in AFI and concludes that both parameters give enough clues to diagnose the etiology.

Key words: *Dengue, Febrile, Malaria, Pediatric*

Acute febrile illness (AFI) is characterized by sudden onset of fever which develops when body is infested by an infectious pathogen. It is the most frequent presenting complaint by the pediatric population in a clinical setting. AFI is a common cause of hospital admission, causing morbidity, and death among children worldwide. Common causes of AFI in India include dengue, typhoid, malaria, and chikungunya fever [1].

Dengue and chikungunya fever are arboviral diseases transmitted by bite of mosquito, namely, *Aedes aegypti* and *Aedes albopictus* that are endemic in tropical countries like India, both present with common symptoms such as fever, body pain, skin rashes, nausea, vomiting, and weakness [2]. Acute arthritis and rashes are more common in case of chikungunya while in cases of dengue; especially in dengue hemorrhagic fever, bleeding and shock may occur due to leakage of plasma.

Dengue virus (DENV) has four serotypes (DENV 1–4) belonging to the genus flavivirus and is one of the most widespread arthropod-borne viral disease [3]. The World Health Organization (WHO) has included dengue in its target list of mostly neglected tropical diseases during the year 2015–2020. However, data of dengue cases are generally underreported in India because the national surveillance systems are not standardized and are based largely on the clinical diagnosis without the much-needed laboratory confirmations [4,5]. The present study was undertaken to analyze the spectrum of AFI in pediatric population along with the evaluation of hematological parameters in the diagnosis of AFI cases using the preset list of laboratory tests. Prognostic implications of the hematological parameters were also considered.

MATERIALS AND METHODS

This cross-sectional study was conducted, over a period of 2 months, in a tertiary hospital of Northern India. Patients from the pediatric outpatient department presenting with AFI formed the subjects of this study. The study was initiated after seeking approval from the Institutional Ethics Committee. An informed consent was taken from parents and/or guardians. A total of 100 children with the complaint of AFI between 2 and 14 years were included in this study. All patients presented with fever, with a maximum duration of 7 days. The children presenting after 5 days of fever or not giving consent were excluded from the study. After atrial fibrillation episode, blood samples from the pediatric patients were taken within 5 days of onset of fever. Blood for acute sera were taken in plain vial and for hematological investigations were collected in ethylenediaminetetraacetic acid vials.

Complete blood counts were done on Sysmex Cell Counter XN 1000. Cases of malaria were confirmed on microscopy or rapid diagnostic test for malaria antigen. The detection of dengue in the acute serum sample was done using non-structural

protein 1 enzyme-linked immunosorbent assay (ELISA) antigen test. Dengue and chikungunya immunoglobulin M antibody test were ELISA based. Liver function test (LFT) was done on Siemen's dimension expend plus biochemistry analyzer (for alkaline phosphatase; aspartate aminotransferase; and alanine aminotransferase). Other causes of fever were assessed using commercial testing kits for typhoid.

Hematological profiles and biochemical investigations of acute febrile cases were carried out and correlated. Hematological evaluation included complete hemogram and peripheral blood smear evaluation on microscopy. Leukopenia was defined as <4000/mm^3 and thrombocytopenia as <150,000/mm^3. LFT was considered deranged if serum glutamic pyruvic transaminase (SGPT) value was >35 IU/L and serum bilirubin value >1.2 mg/dL. Statistical analysis was done. Patient data were tabulated and analyzed using Chi-square method wherever possible (to obtain p-values) to find any statistical correlation between the various parameters of the febrile illnesses. $p<0.05$ was considered to be statistically significant.

RESULTS

A total of 100 febrile patients, between 2 and 14 years of age, were included in the study which comprised 58 (58%) males and 42 (42%) females. Maximum 32 children were from 2 to 4 years age group, 12 each from 4 to 6, 6 to 8, and 8 to 10 years age group, and 16 each from 10to 12 and 12 to 14 years age group. The mean age of the patients was 7.3 years. The maximum number of children was having malaria in 54 (54%) cases followed by typhoid in 28 (28%) cases, dengue in 12%, and chikungunya in 6% of cases.

The patients presented with various clinical features such as fever, vomiting, myalgia, rashes, abdominal pain, vomiting, and arthralgia (Table 1). All patients presented with fever; the maximum duration of fever was 7 days. The most common clinical presentation in majority of the febrile patients apart from fever was headache seen in 83.3% dengue patients and 44.4% in malaria patients. The most common presenting complaints, among typhoid cases, was vomiting, i.e., in 64.3% while in chikungunya, arthralgia was the most common presenting features seen in all the cases (Table 1).

With respect to the hematological parameters (Table 2), relation with hemoglobin level was statistically insignificant for all diseases. The relation with leukopenia was insignificant in case of malaria, dengue, and chikungunya fever (p=0.36). However, it was statistically significant (p=0.004) in cases of typhoid fever. Significant difference was observed between the severity of thrombocytopenia and dengue fever (p=0.01), while for malaria and typhoid fever, it was statistically insignificant (p=0.71 and 0.35, respectively). Due to the limitation in number of chikungunya patients, statistical analysis was not done.

Among the dengue fever patients, raised serum glutamic-oxaloacetic transaminase (SGOT) was the most common finding seen in 58.3% of patients while raised alkaline phosphatase was seen in most (77.7%) of the malaria patients. A total of 57.1% of typhoid patients had raised SGPT while both SGOT and SGPT abnormalities were found in chikungunya patients (Table 3).

DISCUSSION

AFIs are responsible for a huge burden of death and morbidity in developing countries, especially in children, thus causing an

Table 1: Clinical symptoms and signs of children presenting with acute febrile illness

Symptoms	Dengue (%)	Malaria (%)	Typhoid (%)	Chikungunya (%)
Headache	10 (83.3)	24 (44.4)	16 (57.1)	3 (50)
Myalgia	4 (33.3)	20 (37.1)	12 (42.8)	4 (66)
Vomiting	8 (66.6)	28 (51.8)	18 (64.3)	3 (50)
Rashes	6 (50)	6 (11.1)	8 (28.6)	4 (66)
Abdominal pain	8 (66.6)	10 (18.5)	14 (50)	3 (50)
Arthralgia	5 (41.5)	11 (20.1)	10 (35.7)	6 (100)
Bleeding manifestations	4 (33.3)	3 (5.5)	0	0
Jaundice	2 (16.6)	20 (37.1)	5 (17.8)	0
Diarrhea	8 (66.6)	21 (38.8)	18 (64.2)	2 (33.3)

Table 2: Alterations in hematological parameters in acute febrile pediatric patients

Parameter	Dengue (%)	Malaria (%)	Typhoid (%)	Chikungunya (%)
Anemia (Hb <12 mg/dl)	8 (66.6)	26 (48)	18 (64.3)	0
PCV (<45%)	10 (83.3)	49 (90.7)	22 (78.5)	0
Leukopenia (<4000/mm^3)	4 (33.3)	18 (33.3)	20 (71.4)	5 (83.3)
Neutrophils (<40%)	7 (58.3)	19 (35.2)	2 (7.1)	3 (50)
Lymphocytes (>45%)	4 (33.3)	20 (37.1)	8 (28)	2 (33.3)
Platelets (100,000–150,000/µl)	2 (16.6)	15 (27.7)	15 (53.5)	5 (83.3)
50,000–100,000/µl	5 (41.6)	30 (55.5)	13 (46.4)	1 (16.6)
<50,000/µl	6 (50)	9 (16.6)	2 (7.1)	0

Table 3: Alterations in biochemical parameters in acute febrile pediatric patients

Biochemical parameter	Dengue (%)	Malaria (%)	Typhoid (%)	Chikungunya (%)
Serum glutamic-oxaloacetic transaminase (>40 IU/Ml)	7 (58.3)	19 (35.2)	15 (53.6)	6 (100)
Raised serum glutamic pyruvic transaminase (>35 IU/Ml)	6 (50)	25 (46.2)	16 (57.1)	5 (83.3)
Alkaline phosphatase	4 (33.3)	42 (77.7)	13 (46.5)	1 (16.6)
Serum bilirubin (>1.2 mg/Ml)	2 (16.6)	8 (14)	4 (14)	-

enormous loss of healthy life years [6,7]. The most common etiological agents in the South Asian region are dengue, typhoid, and paratyphoid in febrile patients [8,9].

Thrombocytopenia with anemia is an important clue to the diagnosis of malaria in patients with AFI [10-12]. In cases of complicated falciparum malaria, thrombocytopenia is due to disseminated intravascular coagulation along with platelet endothelial activation. In cases of uncomplicated malaria such as *Plasmodium vivax*, etiology is macrophage activation leading to platelet destruction, antiplatelet antibodies, sequestration in non splenic areas, and partly due to pseudothrombocytopenia due to platelet clump formation. Leukopenia is thought to be due to the localization of leukocytes away from the peripheral circulation, splenic sequestration, and other marginal pools [13].

In our study, among 100 patients who presented with fever, dengue was seen in 12% of cases, malaria in 54%, typhoid in 28% of cases, and chikungunya in 6% of cases. This is similar to the study done previously by Dhingra and Mishra which have reported that dengue fever, typhoid fever, and malaria continue to be a serious public health problem in many developing countries [14].

In our study, among the dengue patients, the most common presentations were headache, vomiting, and gastrointestinal symptoms such as abdominal pain and diarrhea. In a previous study, common clinical presentations included fever, conjunctival congestion, and myalgia (81.9%) [15]. In our study, the most common bleeding manifestation was seen in the form of petechiae, in two of the dengue patients, whereas in the previous study, it was also skin bleeding followed by gum bleeding [15].

Constitutional symptoms such as headache, myalgia, cough, rhinitis, and anorexia are more predominant in chikungunya fever. In the present study, arthralgia was the most common presenting feature seen in both the patients of chikungunya followed by myalgia, vomiting, and rashes. In earlier studies, chikungunya was found to be associated with polyarthralgia, headache, and myalgia/arthralgia of greater severity than in other diseases and skin rashes [16].

Transient thrombocytopenia occurs with many systemic infections presenting as febrile illness. It is also a very common manifestation in tropical infections such as malaria, dengue, chikungunya, many viral infections, as well as typhoid fever. In our study, main cause of thrombocytopenia was malaria fever. In earlier studies, Nair *et al*. concluded septicemia as the main cause of febrile thrombocytopenia while in a study done by Gandhi and Akholkar, malaria was found to be the major cause [17,18]. However, a study done by Bhalara *et al*. showed dengue as the main etiology [19]. The current study also found severe thrombocytopenia to be significant for patients with dengue as compared to patients with malaria, typhoid, and chikungunya.

Change in hematocrit of more than 20% and standard hematocrit cutoffs from the previous studies was used as indicators of hemoconcentration for diagnosing and monitoring severe dengue infection [20-22]. In a study done by Jayashree *et al*., a significant association between platelet counts and severity of the disease was seen, suggesting that platelet count can be used as predictive parameters for diagnosing dengue fever [23]. According to de Azeredo *et al*., other contributing factors may include decreased red blood cell deformability and splenic phagocytosis [24]. Bashawri *et al*. suggested that thrombocytopenia may be through peripheral destruction, excessive removal of platelets by splenic pooling, as well as platelet consumption [25].

In the typhoid fever, anemia, leukopenia, and thrombocytopenia are commonly seen due to bone marrow suppression and hemophagocytosis. Anemia was seen in 64.3% of patients of typhoid fever while leukopenia was observed in 71.1%. Mild thrombocytopenia was seen in 16.6% while 41.6% of the patients had moderate thrombocytopenia. However, none of the patients showed any bleeding manifestations. The current study observed leukopenia to be highly significant for patients with typhoid while it was statistically insignificant in patients with dengue, malaria, and chikungunya. Leukopenia was observed in 18% of cases and 11.2% of cases seen in the previous study done by Ahmed and Gupta [26].

The chikungunya patients in the present study had mild decrease in platelet count in five cases and severe thrombocytopenia in one case, whereas Lee *et al*. observed that mean platelet count was within the normal range while dengue patients had platelets in the lower range [27].

Derangement of liver enzymes is often seen in AFI. In dengue fever, aspartate aminotransferase has been found to increase more quickly and tends to peak at a higher level [28]. Liver enzymes SGOT and SGPT were raised in 53.6% and 57.1%, respectively, among the typhoid patients in the present study. In the study by Jagadish *et al*., increased levels of liver enzymes without jaundice were reported and no correlation was found between the occurrence and degree of hepatic enlargement or hyperbilirubinemia with abnormal LFTs [29]. More than one mechanism is believed to be responsible for hepatic injury in typhoid fever. Salmonella endotoxin-induced consumptive coagulopathy, hepatocyte injury, arteritis, direct invasion of the hepatocytes by the organisms, immune complexes, and consumption of complement are believed to contribute to hepatic insult [30-32].

There were few limitations of the study. Our study was conducted in a setting which caters to patients belonging

primarily to the lower or middle socioeconomic strata and the data primarily reflect the situation in this cohort. Our study was limited in terms of sample size for individual diagnosis. The study with larger sample size would help in evaluating the role of these parameters in a better way.

CONCLUSION

Platelet count is a predictive parameter for dengue fever and leukopenia for typhoid fever, thus reflecting a predictive marker for diagnosing these febrile illnesses in endemic areas.

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