Original Article

A clinicoepidemiological study of serologically diagnosed acute febrile illness in a teaching hospital, Kolkata

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Abstract

Introduction: Similar presenting manifestations in early phase and lack of awareness of aetiology of acute febrile illness (AFI) are major challenges in management of AFI. **Material and Methods:** This was a retrospective observational cross-sectional study conducted in the Department of Microbiology, NRS Medical College, from 1 July 2022 to 30 June 2023 in serologically diagnosed febrile patients attending the outpatient department or admitted. Clinical and epidemiological data and laboratory parameters were recorded in a pretested structured questionnaire study tool, and collected data were analysed on MS-Excel sheets with various charts and tables. **Results:** A total of 1711 serologically diagnosed febrile patients showed preponderance of dengue (38.3%), followed by leptospirosis (25%), scrub typhus (23.9%), malaria (12.6%), and enteric fever (1.92%). A majority of cases were male, less than 40 years of age, and from the rural population (73.2%), except in malaria (urban = 79.6%). The mean duration of fever was 9 days. Febrile cases were recorded maximum during the monsoon and postmonsoon periods (66.5%). The common manifestations are fever, headache (46.2%), pain abdomen (7.8%), nausea, and vomiting (9.4%). Thrombocytopenia with bleeding manifestation was higher in dengue (18%) cases. Mortality in dengue cases was recorded with multiorgan dysfunction syndrome (MODS). Scrub typhus cases showed seizure (8.3%) and altered sensorium (5%) due to fatal meningoencephalitis. Fatality in leptospirosis was mostly due to acute kidney injury (29.5%) and Weil's disease (4.4%). **Conclusion:** Misdiagnosis or incorrect diagnosis and delay in initiation of appropriate treatment results in increased morbidity and mortality in AFI. Determination of epidemiological features and clinical manifestations of AFI along with timely correct diagnosis will benefit clinicians in proper treatment initiation, thereby reducing morbidity and mortality.

Keywords: Dengue, leptospirosis, malaria, scrub typhus, typhoid fever

Introduction

Acute febrile illness (AFI) is one of the major illnesses among people seeking treatment in primary care settings. It has varied aetiologies according to geographical distribution.[1] Diagnosis is often based on presenting manifestation, and patients receive empirical therapy due to similar presentation.[2] Studies from South, North, and West India showed major causes of AFI as scrub typhus, dengue, malaria, enteric fever, leptospirosis, chikungunya, Japanese encephalitis.[3-5] A gap in literature exists in the understanding of the clinical and epidemiological characteristics of AFI in eastern India.

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Table 1: Sensitivity and specificity of serological diagnostic kits

Kit Name	Sensitivity	Specificity
Dengue NS1 Ag ELISA (Oscar™)	100%	100%
Dengue IgM Ab EILSA (Standard E™)	98.2%	95.4%
Scrub typhus IgM Ab ELISA (InBios™)	84.0%	94.82%
Leptospira IgM Ab ELISA (Panbio™)	96.5%	98.5%
Malaria RDT kit (Reckon™)	100%*	100%
Widal slide agglutination test (Pathozyme diagnostics™)	91.3%	80.9%

*The sensitivity of Malaria (Pf/Pan) antigen test is compared to microscopic examination with more than 100 parasites per µl of blood. The sensitivity and specificity of all test kits provided here are according to the manufacturer's kit literature.

Table 2: Relevant clinical manifestations and laboratory parameters suggestive of organ dysfunction

Organ system	Clinical manifestation	Laboratory parameter/ investigation
Haematological	Anaemia, Bleeding manifestation	Complete blood count
GI system	Nausea, vomiting, diarrhoea	-
Hepatobiliary system	Icterus, ascites	Liver function test, USG abdomen
Renal system	AKI	Kidney function test
Cardiovascular system	Myocarditis, heart failure	ECG, Echocardiography
Respiratory system	Shortness of breath. Pleural effusion	Chest X Ray
Central nervous system	Altered sensorium, Encephalitis, meningitis	CT scan, CSF study

Identifying pathogens of AFI, clinical manifestations, and adverse outcomes will enable triaging cases for better management at a population scale.

Aim of the Study

The aim of this study was to determine epidemiological factors and clinical presentations of five serologically diagnosed causes of AFI (dengue, malaria, scrub typhus, leptospirosis, and enteric fever) in a teaching hospital, Kolkata.

Materials and Methods

This was a hospital-based observational cross-sectional study conducted in the Department of Microbiology, Nil Ratan Sircar Medical College from 1 July 2022 to 30 June 2023 on febrile patients attending the outpatient department (OPD) or admitted in IPD with fever after approval of the Institutional Ethics Committee (IEC No - NRSMC/IEC/131/2022 Dt. 11/10/2022).

The case definition of AFI was acute onset fever and other symptoms such as headache, diarrhoea, chills, and cough without any obvious focus of infection for less than 14 days duration.[6,7]

Inclusion criteria

1. Serologically diagnosed dengue, malaria, scrub typhus, leptospirosis, and enteric fever cases.
2. Patients who provided written informed consent for this study.

Exclusion criteria

1. Cases of AFI other than serologically diagnosed cases of dengue, malaria, scrub typhus, leptospirosis, and enteric fever.
2. Patients suffering from haematological malignancies, autoimmune disorders, tuberculosis, and SARS CoV-2 and on immunosuppressants were excluded from this study.

Serological diagnostic criteria

- Dengue: Dengue NS1 Ag ELISA (Oscar™) was performed if there was febrile illness within 5 days and IgM Ab ELISA (Standard E™) was performed after 5 days of illness. Dengue NS1 Ag and/or IgM Ab reactive cases and other serologies and nonreactive and blood culture negative cases were included in this study.
- Scrub typhus: Scrub typhus IgM Ab ELISA (InBios™) reactive with other serologies nonreactive and blood culture-negative.
- Leptospirosis: Leptospira IgM Ab ELISA (Panbio™) reactive with other serologies nonreactive and blood culture-negative
- Malaria: Thick peripheral blood smear examination was done with screening of cases, and thin smear was used for species identification of malarial parasites (trophozoites of *Plasmodium falciparum*, *Plasmodium vivax*, or mixed) and RDT kit (Reckon™) (lateral flow immunochromatographic antigen-detection tests) for Pf-HRP II/Pan-pLDH antigen reactive but other serologies nonreactive and blood culture-negative.
- Enteric fever: Blood culture positive for Salmonella Typhi or Salmonella Paratyphi (BacT/Alert3D™ and Vitek2 compact™) and semiquantitative slide agglutination Widal test (Pathozyme diagnostics™) show titre equals or more than of 1:160 for anti-O antibodies and more than of 1:320 for anti-H antibodies with other serologies as nonreactive. [see Table 1 for list of diagnostic kits which were used in this study].

Acute kidney injury (AKI) was defined according to KDIGO criteria[8] as follows:

- Increase in serum creatinine by ≥0.3 mg/dl (≥26.5 µmol/l) within 48 hours or
- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days or
- Urine volume <0.5 ml/kg/h for 6 hours.

According to World Health Organization (WHO), the leptospirosis fact sheet case definition of Weil's disease was presence of jaundice, renal failure, haemorrhage, and myocarditis with arrhythmias in a patient infected with leptospirosis.[9]

Organ involvement in AFI was assessed by presence of or any new appearance of clinical manifestation and biochemical results

suggestive of particular organ dysfunction during the course of the illness and was regularly followed up till their organ dysfunction improved or the patient died due to the illness. [see Table 2 for clinical manifestations and laboratory parameters which were used to assess organ dysfunction].

In our study, diagnosis of AFI was made on the basis of a combination of clinical manifestation, serological results, and relevant other laboratory parameters such as complete blood count, liver function test, and kidney function test profile.

Clinical and epidemiological data and laboratory parameters from patients, who fulfilled inclusion criteria, were recorded in a pretested structured questionnaire study tool. Data generated were collected and compiled in MS-EXCEL sheets, and relevant statistical analysis, for example, calculation of mean, standard deviation, and percentage calculation, was done and represented in the form of various charts and tables.

Results

During the study period, a total of 1711 patients were serologically diagnosed with AFI. A majority of AFI cases suffered from dengue infection (38.3%), followed by leptospirosis (25%), scrub typhus (23.9%), malaria (12.6%), and enteric fever (1.9%). Higher mortality was recorded in leptospirosis (4%) with an overall mortality of AFI of 2.3% [see Table 3]. Most of the malaria cases were caused by *P. vivax* (58.8%), followed by *P. falciparum* (40.8%), and mixed infection was noted in one patient only.

A majority of patients who attended OPD or were admitted were from rural areas of North and South, 24 Parganas, Howrah, Hooghly, and Nadia, except in malaria (79.6% from urban Kolkata). A majority of the patients were less than 40 years (mean = 35.79 years, SD = 21.22) with a male preponderance except in leptospirosis [see Table 4].

Distinctive seasonal distribution of AFI cases was observed, and a marked increase in cases of dengue was noted in post monsoon months. A post-monsoon peak was also seen in malaria, scrub typhus, and leptospirosis cases [see Figure 1].

The time of presentation with fever was longer in enteric fever (mean = 9 days, SD = 2.3), followed by leptospirosis (mean = 7.7, SD = 4.9). The common presentations in AFI cases were headache in dengue (73.12%), malaria (92.41%),

Table 3: Total number of diagnosed AFI cases, distribution of dengue, leptospirosis, scrub typhus, malaria, and enteric cases and respective mortality rates

Number of serologically diagnosed patients of acute febrile illness (AFI) included in this study : 1711 Mortality: 40/1711 (2.3%)
Dengue: 640 (38.3%) Mortality: 6 (0.9%)
Leptospirosis: 428 (25%), Mortality: 17 (4%)
Scrub typhus: 399 (23.9%), Mortality: 12 (3%)
Malaria: 211 (12.6%) Mortality: 4 (2%)
Enteric fever: 33 (1.9%) Mortality: 1 (3%)

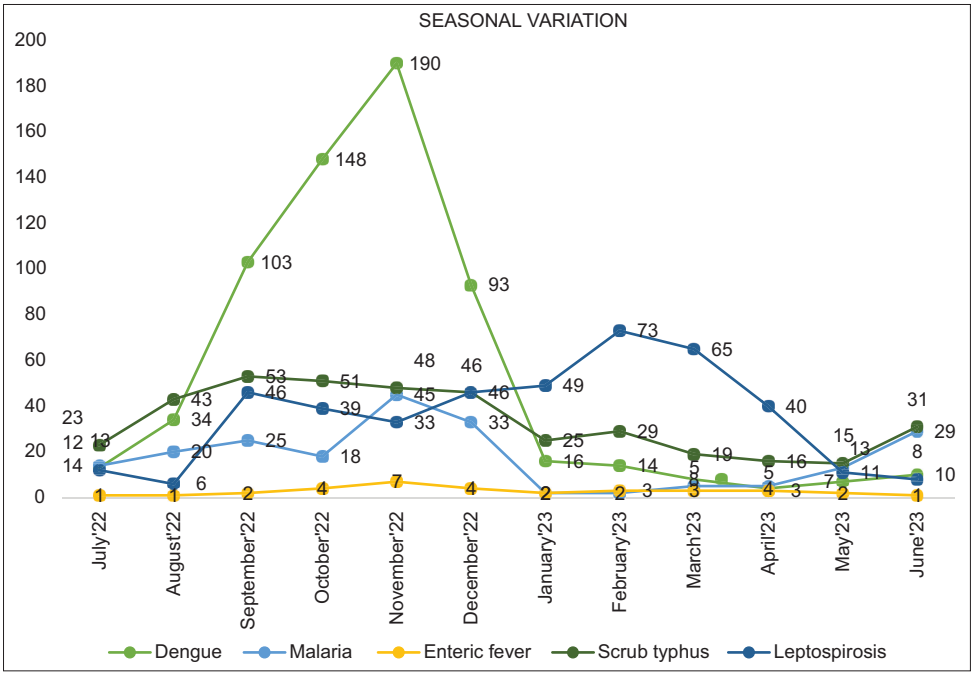

Figure 1: Seasonal distribution of AFI cases

enteric fever (39.39%), scrub typhus (18.29%), vomiting in dengue (17.34%), and scrub typhus (14.53%). Bleeding manifestation (17.96%) was markedly noted in dengue, whereas breathlessness (17.54%), seizure (8.27%), and altered sensorium (5.01%) were prominent symptoms of scrub typhus [see Table 5].

Laboratory investigation showed the mean haemoglobin level decreased in both scrub typhus (Hb – 9.8 g/dl, SD – 1.9) and leptospirosis (Hb – 9.8g/dl SD – 1.4). The total leucocyte count was significantly higher in scrub typhus (mean TLC = 111658/cmm SD = 6289.9) as compared to other causes. In leptospirosis and scrub typhus, increased serum urea and creatinine levels were recorded, which indicated renal involvement. Liver transaminase levels were also higher in leptospirosis as compared to other causes. In dengue, platelet transfusion was required for bleeding manifestation with thrombocytopenia during 5th to 8th day of illness in most of the patients. Thrombocytopenia here is defined by World Health Organization (WHO) as a platelet count of less than or equal to 100,000/μL [see Table 6].

In all AFI cases, the most affected was the haematological system. Hepatic and renal involvement was marked in both leptospirosis and dengue cases, which was also evident by deranged renal and liver function test profiles. In scrub typhus, gastrointestinal (GI) system involvement was prominent (50.62%), which manifested as pain abdomen, nausea, and vomiting. Cardiovascular system (CVS) involvement was seen in severe dengue with shock (8.43%) and in scrub typhus (7.01%), which presented as breathlessness. Severe renal involvement in leptospirosis was seen in the form of AKI (29.5%) and Weil's disease (4.4%). CNS involvement in the form of seizure (8.3%) and altered sensorium (5%) was recorded in scrub typhus cases [see Figure 2].

Discussion

Our study is one of the few studies from East India which characterised spectra of AFI caused by five major pathogens in patients attending OPD or admitted in IPD in a teaching hospital.

The diagnosis of AFIs presents a challenge due to varied aetiologies and fewer diagnostic tools available, even in a teaching

Table 4: Distribution of age, sex, and geographic location across five causes of AFI

	Dengue (*n*=640)	Leptospirosis (*n*=428)	Scrub typhus (*n*=399)	Malaria (*n*=211)	Enteric fever (*n*=33)
Age mean (SD)	25.8 (15.7)	34.8 (22.3)	24.5 (18.7)	39.1 (20.5)	41.1 (21.7)
Male *n* (%)	365 (57.03)	213 (49.76)	223 (55.88)	149 (70.61)	19 (57.57)
Female *n* (%)	275 (42.97)	215 (50.24)	176 (44.12)	62 (29.39)	14 (42.43)
Urban *n* (%)	224 (35)	111 (25.93)	58 (14.53)	168 (79.62)	9 (27.27)
Rural *n* (%)	416 (65)	317 (74.07)	341 (85.47)	48 (20.38)	24 (72.73)

Table 5: Clinical manifestations of AFI cases

	Dengue (*n*=640)	Leptospirosis (*n*=428)	Scrub typhus (*n*=399)	Malaria (*n*=211)	Enteric fever (*n*=33)
Fever duration mean (SD)	5.1 (5.2)	7.7 (4.9)	7.6 (2.7)	5.5 (3.3)	9 (2.3)
Headache *n* (%)	468 (73.12)	33 (8.48)	73 (18.29)	195 (92.41)	13 (39.39)
Pain abdomen *n* (%)	93 (14.53)	16 (4.11)	48 (12.03)	12 (5.68)	3 (9.09)
Nausea *n* (%)	158 (24.68)	22 (5.14)	79 (19.79)	17 (8.05)	2 (6.06)
Vomiting *n* (%)	111 (17.34)	20 (5.14)	58 (14.53)	17 (8.05)	2 (6.06)
Bleeding manifestation *n* (%)	115 (17.96)	13 (3.34)	10 (2.5)	6 (2.84)	Nil
Breathlessness *n* (%)	17 (2.65)	13 (3.34)	70 (17.54)	Nil	Nil
Seizure *n* (%)	8 (1.25)	7 (1.79)	33 (8.27)	Nil	Nil
Altered sensorium *n* (%)	7 (1.09)	17 (4.37)	20 (5.01)	Nil	Nil

Table 6: Laboratory parameters in AFI cases

	Dengue (*n*=640)	Leptospirosis (*n*=428)	Scrub typhus (*n*=399)	Malaria (*n*=211)	Enteric fever (*n*=33)
Haemoglobin g/dl mean (SD)	11 (2.35)	9.8 (1.9)	9.8 (1.4)	10.3 (2.8)	10.6 (2.5)
TLC cells/cmm mean (SD)	9138 (5926.7)	10938 (5962.4)	11658 (6289.9)	8406 (6102.6)	10608 (5393.6)
Platelet cells/cmm mean (SD)	143526 (80497.2)	144321 (99472.8)	149747 (31039.7)	107889 (88029.9)	200000 (11871.4)
Urea mg/dl mean (SD)	49 (47.45)	75 (82.3)	60 (56.9)	36.1 (24.2)	37 (30.8)
Creatinine mg/dl mean (SD)	1.5 (1.3)	2 (1.9)	2 (2.4)	1.17 (1.2)	1 (1.4)
Total bilirubin mg/dl mean (SD)	2.5 (3.6)	3 (6.2)	2 (1.4)	1.2 (1.8)	1 (2.2)
Albumin g/dl mean (SD)	3.2 (0.6)	3 (0.7)	NA*	3.2 (0.6)	3 (0.6)
SGOT U/L mean (SD)	119 (197.1)	223 (525.4)	146 (125)	87 (173.6)	68 (129.5)
SGPT U/L mean (SD)	171 (262.1)	154 (331.4)	176 (326.8)	67 (180.3)	53 (68.7)
ALP U/L mean (SD)	116 (61.1)	191 (229.3)	NA*	162 (163.4)	169 (182.8)

NA*: Not available

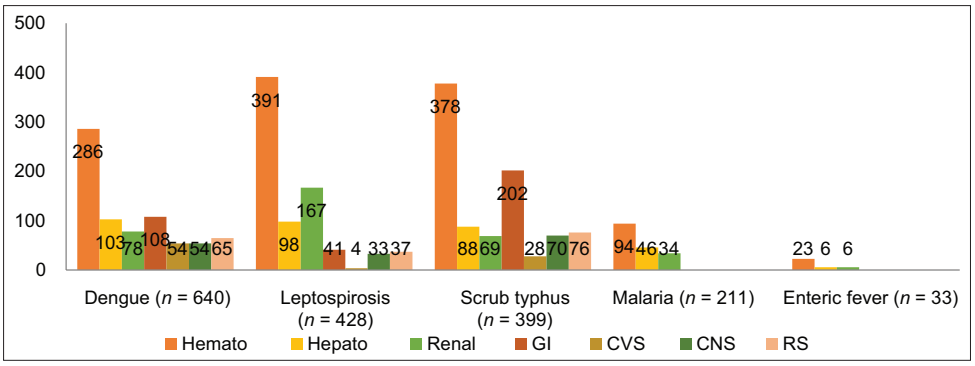

Figure 2: Bar diagram showing organ involvement in AFI cases

hospital like ours. Serological tests are valuable diagnostic tools because they are simple to perform and provide rapid results within few hours of sample receipt.

In the present study, out of 1711 serologically diagnosed AFI cases, males (56.63%) were affected more as compared to females; a majority of patients were in the age group of 25 years to 41 years and the average day of presentation with fever was 9 days. Shelke YP *et al.*[5] and Kumar M *et al.*[10] in their studies of AFI showed that males are predominantly affected, and another study done by Abhilash K *et al.*[3] showed that a majority of the patients were younger than 40 years of age. Shelke YP *et al.*[5] also showed that average day of presentation with fever was 8 days in their study. All these findings are similar with the findings of ours.

In our study, vector-borne diseases, for example, dengue, scrub typhus, leptospirosis, and malaria, had a definitive surge of cases in postmonsoon seasons, which was more prominent in dengue, due to favourable breeding places of vectors. In a similar study by Arvind N *et al.*[11] conducted in South India, similar upsurge of AFI cases was recorded in rainy and autumn seasons.

Our study showed dengue as the predominant cause of AFI, followed by leptospirosis, scrub typhus, malaria, and enteric fever, but previous similar studies showed scrub typhus as a major cause of AFI.[3,5]

Every year, dengue outbreak is a major public health concern in our part of the country with a significant reported morbidity and mortality.[12] In our study, severe dengue cases with bleeding manifestations and thrombocytopenia, between 5th and 8th days of illness, were treated with platelet transfusion with regular platelet level monitoring. This time period of bleeding manifestations in our study is corroborative with a critical phase of severe dengue as defined by WHO.[13]

Scrub typhus and leptospirosis are two important vector-borne causes of AFI with high mortality. Both infections are undiagnosed and underreported because similar clinical manifestations at presentation, lack of awareness, and serological tests for diagnosis of both diseases are only available in teaching hospitals.[14] Delayed diagnosis in both illnesses had poor outcome. In our study, all scrub typhus mortality (3%) was due to acute encephalitis syndrome. In a systematic review and meta-analysis by Alam A *et al.*,[15] the adult case fatality rate of scrub typhus encephalitis was 2.6%, which is similar with our findings (3%). In leptospirosis mortality group, common presentation was Weil's disease, which was characterised by multiple organ system involvement as described before. In our study, AKI was a common manifestation in leptospirosis (29.5%). In a systematic review and meta-analysis on leptospirosis in India, Gupta N *et al.*[16] showed 35% AKI in leptospirosis due to tubulointerstitial nephritis; a similar rate was observed in our study.

Gold standard tests for diagnosing major causes of AFI are unavailable in a majority of resource-limited facilities and also time-consuming. Serological tests also have several drawbacks, e.g. cross-reactivity and misdiagnosis of coinfections as seen in scrub typhus, leptospirosis, and dengue.[14,17] Sensitivity of Widal test increases from second week of illness.[18] To overcome such challenges, syndromic testing by nested multiplex PCR, which has high sensitivity and specificity in detecting major pathogens of AFI at an early phase of illness, will aid early specific treatment initiation.[19]

WHO developed fever management protocol at the community level,[20] but geographical variations of AFI aetiologies pose challenges to implementation of that protocol, thus affecting early, effective management of AFI cases.[21] Study like ours will provide information on the distribution and prevalence of infectious aetiologies of AFIs for formulation of clinical algorithms and management protocols, which is appropriate in our geographic region.

Limitation

In our study, a limited number of pathogens were investigated due to resource constraints and limited laboratory diagnostic capacity. Gold standard tests such as IFA in scrub typhus and MAT in leptospirosis could not be done as these tests are available in selected reference laboratories. Coinfection was not included in our study because serological tests are unreliable in diagnosis of coinfection due to cross-reactivity or missed diagnosis. In enteric fever, we included only cases which are both blood culture-positive and Widal semiquantitative slide agglutination test-reactive, but both these tests have very low sensitivity in early phases of illness,

so we may have missed a number of enteric fever cases in our study. Convalescent phase Widal slide agglutination test was done only in admitted patients. Serial laboratory investigation for organ dysfunction follow-up could only be performed in inpatient cases as most of the outpatient department patients did not turn up for follow-up. P-time and APTT level in all dengue cases with bleeding manifestation were not determined. Due to fund constraint, we could not perform nested multiplex PCR in patients presented with clinical manifestations of AFI; by PCR, we could have detected more cases of AFI at an early phase of illness, which will aid clinicians in informed decision making.

Conclusion

Similar manifestations in the early phase of illness, unawareness about local aetiology, and challenges in serodiagnosis are contributing factors for delay in diagnosis and initiation of appropriate treatment according to aetiology in AFI cases.

Syndromic testing by an accurate diagnostic tool, e.g. Multiplex PCR, which can detect all infections at in a single test setting in early phase of illness with high sensitivity and specificity and appropriate empirical treatment guideline, will have a greater implication in patient management protocols in AFI cases.

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Conflicts of interest

There are no conflicts of interest.

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