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Original Research Article

MIXED TROPICAL INFECTIONS IN CHILDREN PRESENTING WITH ACUTE FEBRILE ILLNESS IN A TERTIARY CARE CENTRE

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ABSTRACT

Background: Acute febrile illness (AFI) is a major cause of paediatric hospitalisation in tropical regions. Endemic infections in these areas complicate diagnosis and management. Mixed infections may present with atypical or severe symptoms. This study aims to determine the prevalence, clinical spectrum, and outcomes of mixed tropical infections in children with AFI. **Materials and Methods:** A descriptive observational study was conducted among 1000 children aged 1 month to 12 years admitted with AFI at a tertiary referral government hospital from July 2018 to June 2019.The patients were clinically evaluated and investigated for dengue, scrub typhus, malaria, enteric fever, and leptospirosis. The patients were grouped as single infections (Group A) or mixed infections (Group B) based on etiological diagnoses, and the data was analysed using chi-square tests. **Result:** Among 1000 children, 81 (8.1%) had mixed infection (group B). The most common combinations were dengue-scrub typhus (44.4%), dengue-malaria (16%), and scrub typhus-enteric fever (9.9%). Mixed infections were significantly more common in older (>5 years) and rural children ($p<0.05$). They were associated with prolonged high-grade fever compared to group A (87.7 vs. 31.0%). The systemic symptoms such as chills, vomiting, arthralgia, and oliguria ($p<0.001$) had higher association in group B patients. Multi-organ involvement including hepatosplenomegaly (79%), renal abnormalities (16%), and thrombocytopenia (90.1%) also was more common in group B patients. Radiological findings revealed increased incidence of hepatosplenomegaly and gall bladder edema in patients with mixed infections. All children with mixed infections recovered, though most required longer hospital stays (7-13 days, 77.8%, $p<0.001$). **Conclusion:** Mixed tropical infections were observed in 8.1% of paediatric AFI cases and were associated with high clinical severity and morbidity. Early recognition and applying appropriate diagnostic tests is important for timely management and improved outcomes.

INTRODUCTION

Acute febrile illness (AFI) is one of the common reasons for paediatric hospital visits in tropical countries, and it is reported in about 1 billion paediatric cases each year globally.[1] Fever in children can be due to infectious causes, such as viral, bacterial, and parasitic infections, or non-infectious aetiologies. However, in tropical and subtropical regions, the vector-borne and water-borne infections like dengue, malaria, scrub typhus, enteric fever and leptospirosis are responsible for most AFI cases.[2] As many infections spread during the same seasons, share similar environmental conditions, and are common in the same areas, it makes it hard for doctors to identify the exact cause of illness based only on symptoms.[3]

Some AFI-causing diseases, such as dengue, have been reported with 7.6 million cases annually in multiple regions. In regions with limited medical facilities there is a difficulty in diagnosis. In such regions, the patient's condition deteriorates rapidly because of delayed or inappropriate therapy.[4] These infections share non-specific features, such as fever, myalgia, vomiting, hepatosplenomegaly, thrombocytopenia, and raised transaminases. The similar symptoms can overlap across various infective diseases and often mimic each other in early infection.[5] Two or more pathogens simultaneously infecting the same patient can further challenge the

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diagnosis. The commonly reported co-infections were dengue-malaria, dengue-scrub typhus, and scrub typhus-leptospirosis. Patients with these co-infections present atypically, or with more severe organ dysfunction, bleeding, or prolonged illness than those with mono-infections. Therefore, recognising co-infections is necessary for a correct treatment plan and supportive care.[6,7]

A Brazilian study identified dengue-malaria co-infection among hospitalised AFI patients and reported a higher prevalence of severe disease among the co-infected population.[7] A South Indian study observed dengue-scrub typhus co-infection with hypoalbuminaemia, early drop in platelets, normal leukocyte counts, and longer hospital stays. In tropical regions, such as India, co-infections are under-recognised and can lead to severe health deterioration. Therefore, timely diagnosis and treatment of coexisting infection is important for preventing adverse conditions, reducing the length of hospital stay and cost of treatment.[8]

Definitive investigations like PCR, culture, paired serology, and Microscopic Agglutination Test (MAT) either takes a longer time, or unavailable, or poorly sensitive in the early stages of the disease. These rapid tests usually identify single-pathogen and may miss co-existing infections.[9] It is necessary to create awareness among the clinician the presence of mixed infection among children presenting with atypical features of AFI. Studies analysing the prevalence and describing the clinical spectrum and outcomes of these co-infections can help clinicians with diagnosis and support management.

MATERIALS AND METHODS

This descriptive observational study was conducted in the inpatient paediatric wards of the largest tertiary government hospital in south India between July 2018 and June 2019.Ethical committee approval was obtained from the institutional ethics committee, and informed consent was obtained from all parents or guardians.

Inclusion and Exclusion Criteria

All children aged 1 month to 12 years who presented with acute febrile illness were included.

Patients who are immunocompromised, have a known focus of infection, have fever of more than 14 days and those who received provisional antibiotic treatment before admission, were excluded.

Methods

A total of 1000 children with AFI were included, who were later categorised into single infection (Group A) or mixed infection (Group B) based on etiological diagnosis after investigations. For each patient, detailed demographic information, clinical history, and examination findings were recorded using a structured proforma. Particular attention was given to age, gender, residence, season of presentation, duration and pattern of fever, associated symptoms, and systemic findings. Under aseptic precautions, 10 ml of venous blood was collected using a 22-G needle for laboratory analysis. All children underwent a set of baseline investigations, including complete blood count with peripheral smear, urine analysis, urine culture and sensitivity, renal function test, liver function test, chest X-ray, ultrasonogram, quantitative C-reactive protein, and non-enteric culture.

Peripheral smear examination for malaria parasites was performed for all cases. In patients clinically suspected of malaria but who were smear-negative, a quantitative buffy coat (QBC) test was performed. Thick and thin blood film microscopy was done, and malaria was diagnosed if they showed a smear positive for parasites or by QBC for either P.vivax or P.falciparum. In patients with fever persisting for more than 5 days, further serological investigations were performed to identify specific tropical infections. These included dengue serology (NS1 antigen or IgM ELISA), scrub typhus IgM ELISA, Widal test, enteric culture for typhoid, and leptospira detection by dark field microscopy (DFM) and microscopic agglutination test (MAT).The diagnostic criteria were positivity for NS1 antigen or dengue IgM ELISA for dengue fever and IgM ELISA positivity for scrub typhus. Leptospirosis was confirmed with a DFM or MAT positivity. A typhoid fever was confirmed if Widal titre was more than 1:160 or had a positive enteric culture. Based on the confirmed etiological diagnosis, 919 children were classified into Group A (single infection) and 81 into Group B (mixed infection).

Statistical Analysis: Data were analysed using IBM SPSS Statistics v27. Continuous variables were expressed as frequencies and percentages. Group comparisons were performed using chi-square tests, and statistical significance was set at $p < 0.05$.

RESULTS

In Group A, the most common single infections were dengue fever (34.5%), scrub typhus (8.1%), enteric fever (15.7%), malaria (3.3%), and leptospirosis (1.4%). Among the 81 children in Group B, the predominant combinations were dengue + scrub typhus (44.4%), dengue + malaria (16%), and scrub typhus + enteric fever (9.9%).

A higher percentage of older children (>5 years) were affected with mixed infection (Group B) compared to single infection (Group A) (64.2% vs. 48.7%; $p = 0.01$). The gender distribution was similar between both the groups ($p = 0.9$). Both the groups had majority of cases during the July-December period (66.7% vs. 65.5%; $p = 0.8$). A rural predominance was observed in mixed infection group B (71.6% vs. 45.2), whereas single infections group A were more common in urban region (54.8 vs. 28.4%, $p<0.001$). the nutritional status in both the groups was comparable (60.5% in B vs 52.9% in A). [Table 1]

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Table 1: Comparison of demographic, seasonal, residential, and nutritional profiles

Parameters	Categories	A (n=919)	B (n=81)	p-value
Age (years)	<1	89 (9.7%)	2 (2.5%)	0.01
	1-5	382 (41.6%)	27 (33.3%)	
	>5	448 (48.7%)	52 (64.2%)	
Gender	Male	441 (48.0%)	39 (48.1%)	0.9
	Female	478 (52.0%)	42 (51.9%)	
Season	July-Dec	602 (65.5%)	54 (66.7%)	0.8
	Jan-June	317 (34.5%)	27 (33.3%)	
Residence	Rural	415 (45.2%)	58 (71.6%)	<0.001
	Urban	504 (54.8%)	23 (28.4%)	
Nutrition	Underweight	359 (39.1%)	26 (32.1%)	0.49
	Normal	486 (52.9%)	49 (60.5%)	
	Obese	74 (8.1%)	6 (7.4%)	

The children in Group B had longer duration of fever (87.7 vs. 31.0%, p < 0.001), whereas the type of fever was similar in both groups. All the children in group B had high-grade fever (100 vs. 86.6%; p < 0.001). The symptoms such as chills (49.4 vs. 19%), arthralgia (50.6 vs. 18.6%), vomiting (63 vs. 41.0%), and oliguria (64.2 vs. 11.3%) were more common in group B than group A (p < 0.001 for each).In the other parameters, shock (13.6 vs. 7.1%, p = 0.034), tachypnoea (22.2 vs. 11.9%, p = 0.007), splenomegaly (79 vs. 12.3%, p < 0.001), altered sensorium (13.6 vs. 3.7%, p < 0.001), facial puffiness (53.1 vs. 18.3%, p < 0.001), coated tongue (29.6 vs. 11.8%, p < 0.001), and hepatomegaly (87.7 vs. 36.6%, p < 0.001) were all more prevalent in group B. [Table 2]

Table 2: Comparison of clinical symptoms and examination

Parameters	Categories	A (n=919)	B (n=81)	p-value
Fever duration (days)	1-6	634 (69.0%)	10 (12.3%)	<0.001
	7-13	285 (31.0%)	71 (87.7%)	
Fever type	Continuous	139 (15.1%)	12 (14.8%)	0.94
	Intermittent	780 (84.9%)	69 (85.2%)	
	Remittent	0	0	
Fever grade	Low	123 (13.4%)	0	<0.001
	High	796 (86.6%)	81 (100%)	
Findings	Chills	175 (19.0%)	40 (49.4%)	<0.001
	Arthralgia	171 (18.6%)	41 (50.6%)	<0.001
	Vomiting	377 (41.0%)	51 (63.0%)	<0.001
	Oliguria	104 (11.3%)	52 (64.2%)	<0.001
	Loose stool	145 (15.8%)	16 (19.8%)	0.35
	Abdominal pain	333 (36.2%)	27 (33.3%)	0.6
Clinical examination	Shock	65 (7.1%)	11 (13.6%)	0.034
	Petechiae	60 (6.5%)	1 (1.2%)	0.056
	Eschar	68 (7.4%)	8 (9.9%)	0.39
	Tachypnoea	109 (11.9%)	18 (22.2%)	0.007
	Abdominal Distension	102 (11.1%)	13 (16.0%)	0.18
	Splenomegaly	113 (12.3%)	64 (79.0%)	<0.001
	Altered Sensorium	34 (3.7%)	11 (13.6%)	<0.001
	Facial Puffiness	168 (18.3%)	43 (53.1%)	<0.001
	Coated Tongue	108 (11.8%)	24 (29.6%)	<0.001
	Hepatomegaly	336 (36.6%)	71 (87.7%)	<0.001

In the investigations, Group B patients had higher rates of leucocytosis (35.8 vs. 13.8%), neutrophilia (16.0 vs. 7.4%), lymphocytosis (56.8 vs. 41.6%), thrombocytopenia (90.1 vs. 54.7%), and anaemia (42vs 22.6%) compared to patients in group A.

In patients in group B, C reactive protein was increased significantly compared to group A (32.1 vs. 15.6%). The other features like albuminuria were also more common in Group B patients (29.6 vs. 12.8%). Most of the urine and blood cultures showed no bacterial growth in either group. Renal function tests were abnormal more commonly in group B (16.0 vs. 1.5%), whereas Liver Function Tests abnormalities were similar between groups (25.5 vs. 24.7 %). [Table 3]

Table 3: Comparison of haematological, biochemical, and microbiological investigations

Investigations	Categories	A(n = 919)	B (n = 81)
TC	Decreased	387 (42.1 %)	15 (18.5 %)
	Normal	405 (44.1 %)	37 (45.7 %)
	Increased	127 (13.8 %)	29 (35.8 %)
Neutrophils	Decreased	326 (35.5 %)	21 (25.9 %)
	Normal	525 (57.1 %)	47 (58.0 %)
	Increased	68 (7.4 %)	13 (16.0 %)
Lymphocytes	Decreased	9 (0.9 %)	12 (14.8 %)

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	Normal	528 (57.4 %)	23 (28.3 %)
	Increased	382 (41.6 %)	46 (56.8 %)
Eosinophils	Decreased	128 (13.9 %)	37 (45.7 %)
	Normal	788 (85.7 %)	43 (53.1 %)
	Increased	3 (0.3 %)	1 (1.2 %)
Platelet Count	Decreased	503 (54.7 %)	73 (90.1 %)
	Normal	404 (44.0 %)	8 (9.9 %)
	Increased	12 (1.3 %)	0
Hb/PCV	Decreased	208 (22.6 %)	34 (42.0 %)
	Normal	606 (65.9 %)	32 (39.5 %)
	Increased	105 (11.4 %)	15 (18.5 %)
Peripheral Smear Suggestive of Sepsis		56 (6.1 %)	1 (1.2 %)
C-Reactive Protein Raised		143 (15.6 %)	26 (32.1 %)
Urine Analysis	Pyuria	39 (4.2 %)	4 (4.9 %)
	Albuminuria	118 (12.8 %)	24 (29.6 %)
Urine Culture	Growth Present	24 (2.6 %)	0
	No Growth	895 (97.3 %)	81 (100 %)
Enteric Culture	S. typhi Positive	2 (0.2 %)	0
	No Growth	423 (46.0 %)	62 (76.5 %)
	Not Done	494 (53.8 %)	19 (23.5 %)
Non-Enteric Culture	No Growth	917 (99.8 %)	81 (100 %)
	Not Done	2 (0.2 %)	0
Abnormal RFT		14 (1.5 %)	13 (16.0 %)
Abnormal LFT		234 (25.5 %)	20 (24.7 %)

Pleural effusion was noted more in group B patients (8.6% vs 6.7%), otherwise the chest X ray findings were comparable in both the groups (91.4 vs. 92.5%). On ultrasound abdomen, abnormalities such as hepatosplenomegaly (61.7 vs. 6.4%) and hepatomegaly with gallbladder oedema (18.5 vs. 9.2%) was noted more frequently in group B. [Table 4]

Table 4: Comparison of radiological and serological investigations

Investigations	Categories	A (n = 919)	B (n = 81)
Chest X-ray	Normal	850 (92.5%)	74 (91.4%)
	Pleural Effusion	62 (6.7%)	7 (8.6%)
	Cardiomegaly with Congestion	3 (0.3%)	0
	Bilateral Pulmonary Congestion	1 (0.1%)	0
	Bilateral Hyperinflation	3 (0.3%)	0
USG Abdomen	Normal	497 (54.1%)	2 (2.5%)
	Hepatomegaly	134 (14.6%)	2 (2.5%)
	Splenomegaly	24 (2.6%)	1 (1.2%)
	PUJ Obstruction	5 (0.5%)	0
	Hepatomegaly with Ascites	10 (1.1%)	0
	Hepatomegaly, GB Oedema, Ascites, Pleural Effusion	105 (11.4%)	11 (13.6%)
	Hepatomegaly with GB Oedema	85 (9.2%)	15 (18.5%)
	Hepatosplenomegaly	59 (6.4%)	50 (61.7%)
WIDAL Test	Positive	144 (15.6%)	23 (28.4%)
	Negative	554 (60.2%)	58 (71.6%)
	Not Done	221 (24.0%)	0
Scrub Typhus Serology (IgM ELISA)	Positive	74 (8.0%)	52 (64.2%)
	Negative	668 (72.6%)	29 (35.8%)
	Not Done	177 (19.2%)	0
Dengue Serology (NS1 / IgM ELISA)	Positive	314 (34.2%)	56 (69.1%)
	Negative	587 (63.9%)	25 (30.9%)
	Not Done	18 (2.0%)	0
Peripheral Smear / QBC (Positive)		30 (100%)	25 (100%)
Leptospira DFM / MAT	Positive	13 (1.4%)	7 (8.6%)
	Negative	668 (72.6%)	74 (91.4%)
	Not Done	238 (25.8%)	0

All the patients in group B recovered completely, in contrast 6 (0.7%) patients died in group A (survival 99.3%) with single infections. The majority of children in group A (70.1%) recovered within 1-6 days, whereas group B (77.8%) required 7-13 days. [Table 5]

Table 5: Distribution of clinical outcomes and hospital stay

Parameters	Categories	A (n=919)	B (n=81)
Outcome	Improved	913 (99.3%)	81 (100%)
	Died	6 (0.7%)	0 (0%)
Hospital stays (days)	1-6 days	644 (70.1%)	15 (18.5%)
	7-13 days	268 (29.2%)	63 (77.8%)
	>14 days	7 (0.8%)	3 (3.7%)

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DISCUSSION

Mixed tropical infections are one of the important causes for AFI in children. In endemic regions multiple pathogens may cause mixed infections. These infections often present with overlapping clinical features, causing diagnostic dilemmas and increased disease severity. The present study evaluated the clinical profile, laboratory findings, and outcomes of mixed tropical infections and compared them with single infections in children admitted with AFI to a tertiary care centre.

Mixed infections were significantly more common in older and rural children, whereas gender, seasonal occurrence, and nutritional status were similar between the groups. Sanan et al,[10] found that the 5-12-year age group was the most commonly affected by tropical fever (62%). They concluded that Dengue, Scrub typhus and Enteric fever were the major etiologies of tropical infections and co existing infections lead to increased severity and multiple complications. Jana et al. observed a high prevalence of scrub typhus and recognised associated coinfections like dengue, enteric fever, urinary tract infections, and malaria. Children who also had dengue were more likely to develop thrombocytopenia. The male-to-female ratio was 1.22:1 and an average age of 5.18 years.[11] They reported anaemia in 81.55% of patients, leucocytosis in 20.39% of patients, thrombocytopenia in 49.51% of patients, and elevated ALT in 57.28% and AST in 63.59% of patients. They also concluded that scrub typhus must be suspected in any febrile child with adverse features even in spite of the absence of eschar.

Ahmed et al,[12] compared dengue mono-infection, malaria mono-infection, and dengue-malaria co-infection, and reported mean ages of 10.64, 5.67, and 7.04 years, respectively. They reported a majority of male children in each group, with no significance (47 vs. 27, 30 vs. 22, and 10 vs. 3). This suggests that mixed infections are common in older rural paediatric populations presenting with AFI to ensure timely diagnosis and management. They concluded that the presence of bleeding in malaria and jaundice in dengue patients should be investigated for co infection.

Megalhaes et al,[7] observed similar symptoms, such as rash, cough, diarrhoea, vomiting, dyspnoea, and jaundice, in both dengue mono-infection and co-infection .While both groups had similar symptoms, the co-infection group was associated with more symptoms at the same time. Similarly, Gautam et al. and Alsedig et al. reported that individuals with malaria and dengue co-infection are commonly associated with fatigue, chills, joint pain, and muscle pain.[13,14] Mehata et al.[15] reported that leptospira and scrub typhus coinfection in many other studies is observed with symptoms such as eschar, hepatomegaly, splenomegaly, and lymphadenopathy. Thus, mixed tropical infections can be characterised by more prolonged fever with severe systemic and multiorgan involvement compared to single infections.

In our study, mixed infections were associated with longer and severe febrile illness, higher rates of systemic symptoms, and severe multiorgan involvement. Mixed infections had higher rates of leucocytosis, lymphocytosis, and thrombocytopenia, along with elevated CRP levels and renal abnormalities, such as albuminuria, and deranged RFTs. Liver dysfunction was comparable between the groups, whereas bacterial cultures were mostly negative.

Chandra et al,[16] analysed dengue and scrub typhus coinfection and observed thrombocytopenia with raised haematocrit. In a similar study, Sapkota et al,[17] observed leucocytosis, thrombocytopenia, elevated bilirubin, and transaminases. Similar to our study, none of the previous studies reported growth in either blood or urine culture. Thus, mixed infections have noticeable haematological and biochemical derangements, such as leucocytosis, lymphocytosis, thrombocytopenia, and renal abnormalities. The absence of bacterial growth in cultures can probably be due to viral or rickettsial aetiology.

In our study, both single and mixed infections showed severe ultrasound abnormalities, particularly hepatosplenomegaly and gallbladder oedema, and were associated with multiple seropositivities. Sriram et al,[18] in a case of scrub typhus with scrub pneumonitis, observed an infiltration in the right lower zone in a chest X-ray report. They reported hepatosplenomegaly in 50% of the paediatric patients with dengue and scrub typhus coinfection. Jana et al,[11] reported that 49.25% of the children had chest X-rays showing nonspecific infiltration, and 4.48% had mild pleural effusion. Further, Rakhecha et al., Sriram et al., and Jose et al. found that most of their cases had positive serological findings.[19,18,20] While recovery rates were good in both groups of our study, mixed infections led to prolonged hospital stays. Ahmad et al,[9] reported 5 deaths in the dengue mono-infection group, 3 in the malaria mono-infection and only 1 in the dengue-malaria co-infection. Var et al,[21] observed mortality in 38.09% of dengue cases with coinfection and 7.17% of dengue mono-infection cases. The mean hospital stay in the co-infection group was 8.1 ± 3.3 days and 5.8 ± 2.3 days in the mono-infection group, and all of these differences were significant ($p < 0.05$). Therefore, longer hospital stays, radiological and ultrasonographic abnormalities, mostly hepatosplenomegaly and gallbladder oedema, along with multiple positive serological tests, are associated with co-infections.

Our findings highlight that mixed tropical infections, although less frequent than single infections, are associated with more severe and prolonged illness, multisystem involvement, and longer hospital stays, particularly among older and rural children. Dengue and scrub typhus co-infection was the most frequent

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combination, followed by dengue-malaria and scrub typhus-enteric fever. Including broad diagnostic testing for multiple tropical pathogens in endemic regions can help timely detection, guide appropriate therapy, and prevent complications in children presenting with AFI.

Limitations

This single-centre, hospital-based study may not fully represent the background population. The mean duration of fever and hospital stay was not analysed. Although the Widal test has lower sensitivity and specificity than enteric culture, it was used for diagnosing enteric fever due to limited resources. Rising titres could not be demonstrated because convalescent sera collection was not feasible due to logistic constraints. The use of serological tests without molecular confirmation may have led to cross-reactivity. Follow-up after discharge was not performed, and long-term outcomes were not assessed.

CONCLUSION

Mixed tropical infections were observed in approximately 8.1% of AFI cases. They are more common in older and rural children and are associated with prolonged fever, severe haematological and renal abnormalities, and longer hospital stays than single infections. Dengue-scrub typhus co-infection was the most frequent combination, followed by dengue-malaria and scrub typhus-enteric fever. Future multicentre studies using molecular diagnostics are necessary to confirm pathogen interactions and assess long-term outcomes in affected children.

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