

Etiological Trends and Epidemiological Profile of Tropical Fever in Children Presenting with Acute Undifferentiated Fever at a Tertiary Care Centre in North India

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ABSTRACT

Introduction: The objective of this study was to determine the etiology of acute undifferentiated fevers (AUF) in hospitalised children with in a tertiary care centre in North India. The various causes of acute undifferentiated fevers included dengue, malaria, scrub typhus, enteric fever, leptospirosis and Chikungunya. The clinical spectrum and therapeutic outcome of these cases was also studied.

Methods: This retrospective study was conducted over a period of 6 months from June 2019 to December 2019. The clinical information of 126 children who tested positive for any of the causes of AUF namely dengue, malaria, scrub typhus, enteric fever, chikungunya and leptospirosis was obtained from the Paediatrics Department. The information was recorded in a predesigned proforma. Various tests performed for the diagnosis of these illnesses were noted. They included dengue NS1 antigen ELISA and IgM ELISA, peripheral blood smear (PBS) for malarial parasite and rapid malarial antigen detection test (RMAT), scrub typhus IgM ELISA, leptospira IgM ELISA, and Chikungunya IgM ELISA.

Results: The diagnosis of AUF were dengue (55.5%; 70/126), malaria (19%; 24/126) and scrub typhus (19%; 24/126), enteric fever (4.7%;6/126) and Chikungunya (1.5%; 2/126). The most common presenting symptom was fever or pyrexia followed by myalgia, generalised aches and pains in the body and vomiting. Commonly observed complications included thrombocytopenia, hepatitis and shock.

Conclusions: Dengue, malaria and scrub typhus are the major causes of AUF in the hospitalised children with dengue being the most prevalent infection. The study further emphasises the need to develop a systematic approach to the diagnosis of AUFs. This should be using a combination of clinical, epidemiological and laboratory parameters, which will be very useful for developing a relevant action plan for treatment and prevention of such fevers in any hospital setup.

Keywords: Acute undifferentiated fever (AUF); Dengue; Malaria; Scrub typhus; Tropical fevers



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INTRODUCTION

Infectious illnesses are the major causes of morbidity and mortality in children, particularly in the tropical countries. Acute undifferentiated fever (AUF) is a febrile illness of less than two weeks' duration, with non specific symptoms and signs such as malaise, myalgia and loss of appetite etc. AUF that are rampant in tropical and subtropical regions are collectively known as tropical fevers.¹ Dengue, malaria, scrub typhus, leptospirosis, enteric fever and chikungunya are some of the common tropical fevers reported in patients from South East Asian countries, including India. Awareness and knowledge about the major febrile illnesses and their co-existence of different tropical fevers which present as AUF is of utmost importance in the treatment and management of children with these illnesses in our setup.²

Diversity exists in the trends and occurrence of these tropical fevers in hospitalised patients as they are greatly influenced by season and geography.³⁻⁵ Some of them are perennial while others demonstrate seasonal variation. These tropical fevers have overlapping clinical presentations, hence, it is imperative that the local epidemiology and etiology of these infections should be known for accurate management of these diseases. There is paucity of data on the etiology and epidemiology of these infections particularly in children. Presently available data on tropical fevers in children is very limited.

This retrospective study was planned and conducted to understand the occurrence of such infections, its epidemiology and therapeutic outcome in children attending a tertiary care teaching hospital over a period of six months.

METHODS

This retrospective study was conducted in the Paediatrics Department in collaboration with the Department of Microbiology at a tertiary care teaching hospital in North India. Ethical clearance was taken from the Institutional Ethics Committee. A waiver for getting informed consent from the patient was obtained as it was a retrospective study (IEC/VMMC/SJH/PROJECT/2019-12/88). The data of the patients (age up to 12 years) admitted in paediatric wards between June to December 2019 and presenting with undifferentiated fever of

minimum five days, was collected from the patient's case records in a predesigned proforma. Those patients who had history of intake of antibiotics or anti-malarial drugs from any outside source or whose complete medical details were not available were excluded from the study. The detailed clinical examination, haematological and biochemical tests were recorded along with the treatment given and the final outcome.

Diagnosis of dengue was done by detection of NS1 antigen and /or specific IgM antibodies by MAC ELISA kits supplied by National Institute of Virology (NIV), Pune, India. Testing for malarial parasite was done by examination of PBS with Giemsa stain and immuno-chromatographic test to detect lactate dehydrogenase (LDH) for *Plasmodium falciparum* and *Plasmodium vivax* and HRP2 for detection of *Plasmodium falciparum* (DiaSys Diagnostics Pvt Ltd, India). For diagnosis of scrub typhus, IgM ELISA (In Bios, USA), for Chikungunya, IgM ELISA (NIV, India) and for leptospirosis, leptospira IgM ELISA (Panbio Pty., Ltd., Queensland, Australia) were used as per the manufacturer's instructions. Enteric fever was diagnosed by detecting IgM antibodies using rapid immunochromatographic test (Med source ozon India) or by Widal test for detection of antibodies against the O and H antigens of *S. typhi* and "H" antigens of *S. paratyphi A*. The completed data was further recorded in Microsoft Excel spreadsheets and the statistical analysis was performed using the SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 4000 samples from suspected cases of AUF were screened in Microbiology Department for dengue, malaria, scrub typhus, enteric fever, leptospirosis and Chikungunya infections. Out of these, 126 samples which satisfied the selection criteria were enrolled in the study. Etiologic agents of tropical fever detected were - Dengue (70 cases), malaria (24 cases); scrub typhus (24 cases); enteric fever (Six cases); Chikungunya (Two cases). There was no case of leptospirosis. Among 126 patients, 79 were males and 47 were females. The mean age of study population was 6.94 years. Epidemiological profile and clinical features of the patients are presented in Table 1.

Table 1. Clinical and epidemiological profile of Patients with Tropical fever

Clinical feature	Dengue (N = 70)	Enteric fever (N = 60)	Scrub (N = 24)	Malaria (N = 24)	Chikungunya (N = 2)	Total (N = 126)	Total %
Male / Female	40/30	4/2	16/8	18/6	1/1	79/47	
Age (Years)							
< 1	4/2	0/0	0/0	1/0	0/1	5/3	6.34%
1 - 5	10/9	2/1	7/2	5/2	0/0	24/14	30.15%
> 5	26/19	2/1	9/6	12/4	1/0	50/30	63.49%
Symptoms							
Fever (Days)							
Fever (Days)	58	6	18	24	2	108	85.71%
< 5	38	2	2	4	0	46	36.50%
5 - 10	17	2	8	12	1	40	31.74%
> 10	3	2	8	8	1	22	17.46%
Breathing difficulty	0 (0)	0 (0)	1 (4.2)	4 (16.6)	0 (0)	5	3.96%
Seizure	5 (7.14)	0 (0)	2 (8.33)	0 (0)	0 (0)	7	5.55%
Bleeding	6 (8.6)	0 (0)	2 (8.33)	2 (8.33)	0 (0)	10	7.93%
Chills/rigors	0 (0)	0 (0)	0 (0)	14 (58.3)	1 (50)	15	11.90%
Headache	5 (7.14)	1 (7.2)	4 (16.6)	6 (25)	0(0)	16	12.70%
Pain abdomen	35 (50)	1 (1.66)	7 (29.16)	10	1 (50)	54	42.85%
Vomiting	42	3	8	12 (41.6)	1	66	52.38%
Body Pain	46 (65.7)	2 (3.33)	6 (25)	14 (58.3)	2 (100)	70	55.56%
Signs							
Lymphadenopathy	0(0)	0 (0)	0 (0)	0(0)	0 (0)	0	0
Eschar	0(0)	0 (0)	2 (8.33)	0(0)	0 (0)	2	1.58%
Meningeal signs	1(1.42)	3 (5)	0(0)	0(0)	0 (0)	4	3.17%
Jaundice	1 (1.42)	0 (0)	2 (8.33)	4 (16.6)	0 (0)	7	5.55%
Pericardial effusion	6 (8.57)	0 (0)	2 (8.33)	0(0)	0 (0)	8	6.34%
Crackles/wheeze	5 (7.14)	0 (0)	2 (8.33)	2 (8.33)	0 (0)	9	7.14%
Signs of raised ICT	7 (10)	1 (1.66)	2 (8.33)	1 (4.16)	0 (0)	11	8.73%
Edema	8 (11.4)	2 (3.33)	3 (12.5)	0(0)	0 (0)	13	10.31%
Pleural effusion	10 (14.2)	0(0)	2 (8.33)	1 (4.16)	0 (0)	13	10.31%
Ascites	11 (15.7)	1 (1.66)	1 (4.16)	1 (4.16)	0 (0)	14	11.12%
Splenomegaly	1 (1.42)	2 (3.33)	2 (8.33)	10 (41.6)	0 (0)	15	11.90%
Rash	15 (21.42)	1 (1.66)	3 (12.5)	0(0)	2 (100)	21	16.66%
Pallor	4 (5.71)	3 (5)	4 (16.6)	9 (37.5)	0(0)	20	15.87%
Tachypnea/ chest retraction	8 (11.4)	2 (3.33)	6 (25)	4 (16.6)	0(0)	20	15.87%
Altered sensorium	14 (20)	3 (5)	8 (33.3)	4 (16.6)	0(0)	29	23.01%
Evidence of shock	21(30)	3 (5)	6 (25)	7 (29.1)	0(0)	37	29.36%
Hepatomegaly	20 (28.57)	5 (8.33)	14 (58.3)	13 (54.2)	0(0)	52	41.26%

The observed haematological alterations were thrombocytopenia in 74 cases. Thrombocytopenia was observed in 79% (19/24) of the patients with scrub typhus, 62% (44/70) of the dengue cases and 45% (11/24) of patients with malaria. Pancytopenia was seen in 8/126 cases (6.4%). Out of these, four

were positive for dengue, three for scrub typhus and one for malaria.

Biochemical, haematological and other laboratory parameters of all the cases have been shown in Table 2.

Table 2. Laboratory investigations of patients with Tropical fevers

Biochemical Parameters		Total (N=126)	Total Percentage (%)
Aspartate amino-transferase (AST) > 40 IU/l	< 2x	26	20.63
	2x - 4x	23	18.25
	> 4x	35	27.7
Alanine transaminase (ALT) > 40 IU/l	< 2x	19	15.07
	2x - 4x	10	7.93
	> 4x	29	23.01
Bilirubin (>1.2mg %)		23	18.25
Altered coagulation profile (PT/INR)		33	26.19
Raised Creatinine (>1mg/dl)		8	6.34
Hematologic parameters		Total (N=126)	Total Percentage (%)
Hemoglobin (gm %)	8 to 10	45	35.71
	6 to 8	21	16.6
	< 6	3	2.8
Total leucocyte count (per cu.mm)	< 4000	10	7.94
	4000 - 11000	76	60.32
	> 11000	40	31.74
Platelets (per cu.mm)	100000-150000	11	8.73
	50000-100000	28	22.22
	20000-50000	23	18.25
	<20000	12	9.52
Pancytopenia		8	6.34

Etiologic agents detected were dengue (55.5%; 70/126), malaria (19%; 24/126); scrub typhus (19%; 24/126), enteric fever (4.7%; 6/126) and chikungunya (1.5%; 2/126). Co-infections of malaria and enteric fever were recorded in eight, dengue and malaria in five, dengue and enteric fever in three, malaria and scrub typhus in two and enteric fever and scrub typhus in two patients. Not a single case of leptospirosis was reported in our study. Out of 126 patients, 118 were successfully treated and discharged, and eight succumbed. All eight patients who died were dengue positive.

Table 3. Complications observed in patients with Tropical fever

Complication	No of cases (%)
Hepatitis	58(46.03%)
Shock	28(22.22%)
CHF	11(8.73%)
Signs of raised ICT	11(8.73%)
HLH	10(7.93%)
DIC	10(7.93%)
Respiratory failure	10(7.93%)
Meningoencephalitis	6(4.76%)
Acute renal failure	5 (3.96%)
Pneumonia	5 (3.96%)
ARDS	4(3.17%)
Cardiac dysfunction	2(1.58%)

Lumbar puncture was done in 26 patients who showed signs of raised ICT or meningitis. Abnormal CSF findings (raised proteins and decreased sugar) were obtained in six patients. All CSF cultures were sterile. Hepatitis, shock, haemophagocytic lymphohistocytosis (HLH), DIC, ARDS, CHF and raised ICT were some common complications observed in the present study. HLH, an atypical complication was observed in 10 cases (Four dengue, three scrub typhus, two malaria and one enteric fever). Various other complications found have been depicted in Table 3.

DISCUSSION

Tropical fevers pose a major problem in the tropical regions of the world. India constitutes a major chunk of tropical infections, which are either vector borne or food borne. These tropical fevers often present as AUF with overlapping symptoms and signs and hence making it difficult to diagnose clinically.

In our study, amongst the paediatric patients with acute febrile illness and its systemic manifestations, dengue, malaria and scrub typhus were found to be the commonest etiologies followed by enteric fever and Chikungunya. These results are comparable to other studies from India and other South East Asian countries with slight variable results.⁶⁻¹⁰ Such

variation may have resulted because of various geographical status and local endemicity. A high number of dengue cases in our study could be attributed to the endemicity of dengue in our region.

In regards to clinical presentation, fever was the most common presenting feature, followed by myalgia / generalised body pain, vomiting and rashes. We noted that fever was the presenting feature in all patients with malaria and enteric fever. Fever was present in 58/70 (82.9%) cases of dengue and 18/24 (75%) cases of scrub typhus. This implies that some of the cases of dengue and scrub typhus may have been afebrile at the time of presentation. Similarly chills and rigors were also observed in 15/24 (62.5%) cases of malaria.

Rash was the predominant sign of dengue 15/70 (21.4%) and chikungunya (2/2) patients. Eschar, which is a pathognomonic sign of scrub typhus was seen only in 2/24 (8.3%) cases, which is much less than that published by other workers from our region.¹¹ Although bleeding manifestations were observed in more number of cases of dengue 6/70 (8.6%), the percentage of cases presenting with bleeding manifestations remained same for both scrub typhus (8.33%) and malaria (8.33%).

There are published case reports / series where the CNS involvement presenting either as meningitis and / or encephalitis has been seen in patients with dengue and scrub typhus.¹²⁻¹⁴ We found CNS manifestations in 50% scrub typhus cases and 38.6% of dengue cases. CNS manifestations that were observed were seizures, altered sensorium, raised intra cranial pressure and meningeal signs.

We found thrombocytopenia in 79% of patients with scrub typhus, 62% of dengue cases and 45% of patients with malaria. Pancytopenia was seen with remarkable predominance in dengue and scrub typhus as compared to malaria. The possible underlying causes of pancytopenia in tropical fevers are bone marrow hypoplasia, haemophagocytic syndrome or secondary to microangiopathic haemolytic anaemia. Haemophagocytic syndrome (HPS) is one of the key players in the pathogenesis of pancytopenia in various tropical fevers.¹⁵

HLH or HPS is suspected in patients presenting with high-grade fever, splenomegaly, pancytopenia and multi-system involvement. The findings of raised serum lactate dehydrogenase (LDH), ferritin and triglyceride and / or a low fibrinogen further increases the probability of HLH. Karnad et al. found an association of HLH with the tropical fevers like dengue, malaria, tuberculosis, hepatitis A, enteric fever, rickettsia, leptospirosis, chikungunya, meningococemia, HIV, infectious mononucleosis etc.¹⁵ In our study HLH was seen in almost all reported tropical fevers except in chikungunya. These findings suggest that HLH may complicate any of the cases presenting with AUF.

Some studies have tried to examine the various clinical and laboratory parameters to differentiate between tropical fevers, while others have tried to develop a scoring system to differentiate between the various causes of undifferentiated fevers.^{8,16} Some studies have reported leukocytosis, elevated alanine aminotransferase (ALT), elevated aspartate aminotransferase (AST), low serum albumin as significant predictors of scrub typhus when compared to other AUF.^{8,16} Similar findings were observed in our study also. In our study leukocytosis was observed in 33%, while elevated AST and ALT were observed in 75% and 67% of the patients with scrub typhus respectively. Such phenomenon in scrub typhus can be attributed to intrahepatic sinusoidal endothelial vasculitis caused by *Orientia tsutsugamushi*.^{17,18} Varying degrees of liver involvement in tropical fevers may be explained from hepatocyte apoptosis caused directly by the infective agent, impaired liver perfusion resulting from fluid leakage, oxidative stress or immune mediated injury.

In our study, the common complications were hepatitis, shock, CHF, raised ICT, DIC along with some atypical complications like HLH, meningoencephalitis, renal failure and ARDS. Besides various complications, there were total eight patients who had died. We also noted that all the mortality in our study were due to dengue. Dengue is known to be a relatively more fatal disease among AUF, and the higher prevalence of dengue in our study may have led to such finding.

This retrospective study had certain limitations. As this study is a single centric study, there can be a patient population bias in the patient selection and their referral pattern. Gold standard tests for these various AUF could not be performed for confirmation due to limited resources. Since our hospital is a tertiary care centre, the referral bias may be far higher for the reported complication rates.

CONCLUSIONS

Dengue, malaria, scrub typhus, enteric fever etc are the common tropical fevers found in the children in our region. This retrospective study highlights the emerging problem of scrub typhus in our setup. Details of the various biochemical and

haematological parameters along with atypical manifestations like HLH observed in the children in the present study will greatly assist the clinicians by increasing their awareness of the varying manifestations of these tropical fevers. This study and similar data on AUF in the future should be very useful in developing a relevant action plan to address this public health issue.

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