

Research Article

Prevalence of Concurrent Infections among Tropical Fevers in Pediatric Population-A Hospital Based Study

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Keywords

- Concurrent infection
- Tropical fever
- Acute undifferentiated fever (AUF)

Abstract

Introduction: Concurrent infections among tropical fevers like Dengue, Scrub typhus, Malaria, Chikungunya, Enteric fever and Leptospirosis have recently been recognized as an emerging problem. The objectives of this study were to determine the prevalence of concurrent infections among above mentioned tropical fevers in children hospitalized in an apex medical centre in North India and to correlate the epidemiology and therapeutic outcomes.

Methods: This hospital based retrospective study was conducted over a period of 6 months, from June 2019 to December 2019. The clinical records of 126 patients who had been admitted in paediatric wards with tropical fevers were retrieved and investigated for the presence of concurrent infections.

Results: Twenty six out of 126 patients were found to have different coinfections. The most common coinfection was Enteric fever with Malaria in eight patients while coinfection of Malaria and Scrub typhus was reported in six patients. Coinfections of Dengue with Malaria and Dengue along with Enteric fever were recorded in three patients. Whereas Dengue and Scrub typhus and Dengue with Chikungunya were observed in two (2) and one (1) patient respectively. Scrub typhus along with Enteric fever coinfection was observed in two (2) patients. Triple infection of Scrub typhus, Dengue and Plasmodium vivax Malaria was detected in one (1) patient. Thrombocytopenia, hepatitis and shock were the frequently noted complications in this study.

Conclusions: Dengue, Scrub typhus, Malaria, Chikungunya and Enteric fever were the major aetiologies of tropical fevers which existed as coinfections. This resulted in the increase in severity of these infections along with different complications. Point of care testing for these infections greatly aids in the early diagnosis with significantly improved outcome.

INTRODUCTION

In the recent years, concurrent infections with different vector borne diseases causing Acute undifferentiated fever (AUF), are being increasingly recognized worldwide, especially in tropical and subtropical regions because of their recurring outbreaks. Most of these tropical fevers which include, Dengue, Scrub typhus, Malaria, Chikungunya, Enteric fever and Leptospirosis have become endemic in many areas with millions of cases occurring every year.^{1,2}

Precise information about the prevalence, major aetiologies and clinical outcome of the various co-infections presenting as Acute undifferentiated fever (AUF), is important for their effective management and to reduce the patient morbidity and mortality, especially in South East Asian countries like India [1]. Currently available literature is limited to the presence of individual infections in the patients such as Dengue, Enteric fever, Malaria and Scrub typhus. However there is paucity of data as regards the prevalence of coinfections among the Acute undifferentiated tropical fevers and the clinical profile of the patients presenting

with concurrent tropical infections. Due to the overlapping clinical and laboratory features, it is important to rule out all the differential causes of AUF. The present retrospective study is an attempt to understand the prevalence of concurrent tropical infections, epidemiology and therapeutic outcome in children attending a tertiary care teaching hospital in North India over a period of 6 months (June 2019 to December 2019).

MATERIAL AND METHODS

This retrospective study was conducted in the Paediatric Department of a tertiary care centre in North India in collaboration with the Microbiology Department of the centre. Ethical clearance was obtained from the Institutional Ethics Committee (IEC) (IEC/VMMC/SJH/PROJECT/2019-12/88). A total of 4000 samples of paediatric patients suspected of having AUF were received in the Laboratory of the Department of Microbiology over a period of 6 months (June 2019 to December 2019). The data of the admitted patients (aged 1month to 12 years) presenting with Acute undifferentiated fever (AUF) of minimum 5 days, who were positive for any of the above mentioned tropical fevers

(Dengue, Scrub typhus, Malaria, Chikungunya, Enteric fever or Leptospirosis) was collected in a pre designed proforma from the patient's case sheets. The case definitions of Dengue fever, Scrub typhus, Malaria, Chikungunya, Enteric fever and Leptospirosis were taken as per the standard guidelines [2-7]. The observation of the presence of more than one infective aetiology in the patients among the outlined infections was considered as a coinfection. The patients who had a history of taking antibiotics from outside or anti-malarial drug intake or non availability of complete medical details as per designed proforma were excluded from the study.

All the serological tests were performed as per the manufacturer's instructions. ELISA was performed to detect Scrub typhus and Leptospira specific IgM levels (InBios International Inc, USA). For diagnosis of Dengue, NS1 antigen and/or specific IgM antibodies were detected by MAC ELISA kits supplied by National Institute of Virology (NIV), Pune, India. Chikungunya was diagnosed using IgM ELISA (NIV, India) kit. Testing for Malaria was done by examination of peripheral blood smear (PBS) with Giemsa stain and RMAT (Rapid Malaria Antigen Test), immuno-chromatographic test which detects HRP2 and LDH (YBIO, India). Enteric fever was diagnosed by detection of IgM antibodies using rapid immunochromatographic test (Med source Ozon India. Data of all the positive cases of Dengue, Scrub typhus, Malaria, Chikungunya, Enteric fever and Leptospirosis in children (up to 12 years) was compiled and analysed. The details of the clinical, hematological, biochemical and treatment details as well as the final outcome of the treatment and medical management were also collected in pre- design proforma. The data was recorded in Microsoft Excel spreadsheets and the statistical analysis was done using the SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA). Proportions of the studied groups were expressed as percentages

RESULTS

During the study period, Dengue fever was diagnosed in 70 (55.5%), patients, Scrub typhus was diagnosed in 24 (19%) patients, *P. vivax* malaria in 24 (19%), Enteric fever in six (4.7%), patients and chikungunya was diagnosed in two (1.5%) patients. Amongst these AUF cases, concurrent coinfections were noted in 26 patients who were enrolled in the study. The distribution of different coinfections is shown in **Table 1**. Demographic characteristics and clinical presentations of cases with

coinfections are presented in **Table 2** and laboratory details are shown in **Table 3**.

Average duration of hospital stay was 13 days (8-21 days). Mechanical ventilation was provided to 4/26 (15%) children. A total of 24 patients were successfully treated and discharged. However two (2) patients, one (1) with concurrent infection of Dengue with Malaria and another with Dengue and Scrub typhus succumbed to the infections.

DISCUSSION

Concurrent infections with different vector borne diseases causing acute undifferentiated fever (AUF) have become problematic in the tropical regions. Though India is an epicentre for tropical fevers, yet there is a paucity of data on the aetiology and epidemiology of these concurrent infections particularly in children [8]. Concurrent co infection with more than one aetiological agent leads to an illness with overlapping clinical manifestations, which poses a major challenge in the diagnosis and management of such cases. Hence, it is important that the local epidemiology and aetiology of these infections should be known in order to offer guidance for the early and accurate management of these diseases. Keeping this in mind, this retrospective study was conducted to understand the incidence of such concurrent infections, their epidemiology and therapeutic outcome in hospitalised children over a period of 6 months.

In our study, amongst paediatric patients with acute febrile illness and their systemic manifestations, Dengue (55.5%; 70/126), Scrub typhus (19%; 24/126) and Malaria (19%; 24/126) were found to be the most common aetiologies followed by Enteric fever (4.7%; 6/126) and Chikungunya (1.5%; 2/126). These results are comparable to other studies from India and other south east Asian countries with some differences in the relative incidence [8-12]. The geographical distinction observed among these studies may explain the variations in the aetiology. High number of Dengue cases in our study could be attributed to the endemecity of Dengue in Delhi.

The prevalence of concurrent infections reported in this study was around 20%, which is much higher than found in the previous studies [1]. Dengue is endemic in Delhi, so maximum types of coinfections were found to be associated with Dengue. Dengue fever and *P. vivax* malaria coinfections were noted in 3 (11%), patients, Dengue and Enteric fever in 3 (11%), Dengue and Scrub typhus in 2 (8%), Dengue and Chikungunya in one (4%) patient and a triple infection consisting of Malaria, Dengue and Scrub typhus in one (4%), patient. Scrub typhus is commonly reported from sub Himalayan regions of the country. However it remains under diagnosed in our region due to the notion that Scrub is a disease of heavily forested areas with Scrub vegetation. Concurrent infection of Scrub typhus and Malaria were observed in 6 (23%), patients, Scrub typhus and Enteric fever in 2 (8%), Scrub typhus and Dengue 2 (8%), patients. It was also observed that concurrent infection of Malaria and Enteric fever occurred in 8 (30%) cases. Clinical features like fever, body pain / myalgia, vomiting, rashes, seizure, breathing difficulties and hepatosplenomegaly were the most common presenting features in all concurrent infections. Rashes were more frequently noted in Dengue and Scrub typhus coinfection

Table 1: Distribution of the different coinfections among patients.

S. No.	Coinfection	No of cases
1	Scrub typhus + Malaria	6
2	Enteric Fever + Malaria	8
3	Dengue + Enteric Fever	3
4	Scrub typhus+ Enteric Fever	2
5	Scrub typhus+ Dengue	2
6	Dengue + Malaria	3
7	Dengue + Malaria+ Scrub typhus	1
8	Dengue +Chikungunya	1
	Total	26

Table 2: Clinical epidemiological profile of patients with concurrent Tropical fever.

Clinical Parameters	S+M (N=6)	E+M (N=8)	D+E(N=3)	S+E (N=2)	S+D (N=2)	D+M (N=3)	D+M+S (N=1)	D+C (N=1)	Total (N=26)	Percentage
Male/Female	4/2	4/4	2/1	1/1	1/1	2/1	1/0	1/0	16/10	20.63%
Age(Years)										
<1	0	0	0	0	0	0	0	0	0	
1-5	1	3	2	1	1	2	0	0	10	
>5	5	5	1	1	1	1	1	1	16	
Symptoms										
Fever (Days)										
<5	0	1	1	0	0	2	0	0	4	
5-10	2	3	1	1	0	1	1	0	9	
>10	4	4	1	1	2	0	0	1	13	
Chills/rigors	0	1	0	0	0	0	0	0	1	3.84
Headache	4	5	1	1	0	1	0	0	12	46.15
Body Pain	3	6	2	1	2	2	1	1	18	69.23
Pain abdomen	2	3	2	1	1	1	1	1	12	46.15
Vomiting	3	4	2	1	1	1	1	1	14	53.84
Seizure	1	0	0	1	0	0	0	0	2	7.69
Bleeding	0	1	1	0	1	0	0	0	3	11.53
Breathing difficulty	1	2	1	1	1	0	0	0	6	23.07
Signs										
Rash	1	0	1	0	1	0	0	0	3	11.53
Pallor	2	4	1	1	1	1	0	0	10	38.46
Jaundice	2	1	1	1	0	0	0	0	5	19.23
Lymph adenopathy	0	0	1	0	0	0	0	0	1	3.84
Edema	0	0	0	1	1	0	0	0	2	7.69
Ev. Of Shock	1	1	0	1	0	0	1	0	4	15.38
Tachypnea/ retraction	2	1	1	1	1	0	0	0	6	23.07
Crackles/wheeze	0	1	1	1	1	0	0	0	4	15.38
Hepatosplenomegaly	4	5	2	2	2	0	1	0	16	61.53
Ascitis	0	0	1	1	1	0	0	0	3	11.53
Altered Sensorium	1	1	0	1	0	0	0	0	3	11.53
Sign of rise ICT	1	0	0	1	0	0	0	0	2	7.69
Meningeal sign	1	0	0	0	0	0	0	0	1	3.84

Table 3: Laboratory investigations of patients with concurrent Tropical fever.

Laboratory parameters	S+M (N=6)	E+M (N=8)	D+E (N=3)	S+E (N=2)	S+D (N=2)	D+M (N=3)	D+M+S (N=1)	D+C (N=1)	Total
AST (>40 IU/l)									
<2x	0	1	0	0	1	1	0	0	3
2x- 4x	1	2	1	0	0	0	0	0	4
>4x	1	3	2	2	1	1	1	1	12
ALT (>40 IU/l)									
<2x	1	1	0	0	0	0	0	0	2
2x-4x	0	1	0	1	1	0	0	1	4
>4x	1	2	2	1	0	1	1	0	8
Bilirubin (1.2mg %)	1	1	0	0	0	0	1	0	3
Serum Sodium (<130meq/l)	4	5	1	1	1	1	0	0	13
Altered coagulation profile (PT/INR)	0	1	1	1	0	0	1	0	4
X- ray Chest (Pneumonia/ pleural effusion)	0	0	0	1	1	0	0	0	2

as compared to other cases of concurrent infections.⁵ Prolonged fever, thrombocytopenia, anemia, renal failure and jaundice were found to be more pronounced in Malaria/Dengue coinfections. Dengue/Chikungunya coinfections often result in diarrhea, internal bleeding, hepatomegaly and an overall increase in disease severity. High grade fever was the only distinguishing feature of Malaria/Chikungunya coinfection. More such studies are required to create a consensus about disease outcome in cases of various co infections [13].

Thrombocytopenia (19/26;73%), hepatitis (14/26;53%), shock (4/26;26) were the frequently noted complications in this study as compared to others studies (Figure 1) [2,14]. This study also highlights the atypical haematological finding, thrombocytopenia (19/26;73%), anaemia (10/26;38.46), pancytopenia (3/26;11%) and hemophagocytic lymphohistocytosis (HLH) (3/26,11%) (Figure 1). Thrombocytopenia has been observed in Dengue, Malaria and Scrub typhus cases. Anaemia and pancytopenia were seen with remarkable predominance in Scrub and Dengue as compared to Malaria. The possible underlying causes of pancytopenia in tropical infections are bone marrow hypoplasia as evidenced by the low reticulocyte count, hemophagocytic syndrome or secondary to microangiopathic hemolytic anemia. Hemophagocytic syndrome (HPS), is one of the key players in the pathogenesis of pancytopenia during various tropical infections like Dengue, Scrub typhus and Malaria [15]. HLH is suspected in patients presenting with high-grade fever, splenomegaly, pancytopenia and multisystem involvement. The findings of raised LDH, ferritin and triglyceride and/or a low fibrinogen further increase the probability of HLH. Kodan et al., found an association of HLH with the following Tropical diseases: Dengue, Malaria, Tuberculosis, Hepatitis A, Enteric fever, Rickettsial diseases, Leptospirosis, Chikungunya, Crimean-Congo Haemorrhagic fever, Meningococemia, HIV and Infectious mononucleosis [16]. In our study HLH was seen in 06/26 (11.6%), cases of coinfection (Figure 1). These findings suggest that it is important to keep the possibility of a secondary HLH when one is dealing with a

Tropical fever with a pan or bicytopenia especially in cases of a coinfection as it would require specific therapy for Secondary HLH in addition to the pathogen specific treatment.

Interaction of multiple pathogens within a host may potentially result in several different outcomes. Firstly, if the co infecting organisms are dependent on same tissues for the causation of infection, then that particular host tissue may have to deal with multiple pathogens at the same time as compared to that in cases of

mono- infections. Secondly, the immune effector mechanisms triggered by one pathogen may weaken or divert the host immunity leading to a severe outcome or an increased resistance to therapy [13].

This retrospective study had certain limitations like -selection bias, small sample size and absence of a control study group. Hence further studies are required to correlate the clinical features, the haematological and biochemical parameters in order to establish an accurate and timely diagnosis of concurrent tropical infections.

CONCLUSION

Dengue, Scrub typhus, Malaria and Enteric fever and Chikungunya were the most important and major aetiologies of Tropical infections. These infections when they exist as coinfections, present with overlapping clinical features which leads to increased severity of the disease with multiple complications in the paediatric patients. Point of care testing for these coinfections or multiple infections helps in early diagnosis and improved outcome.

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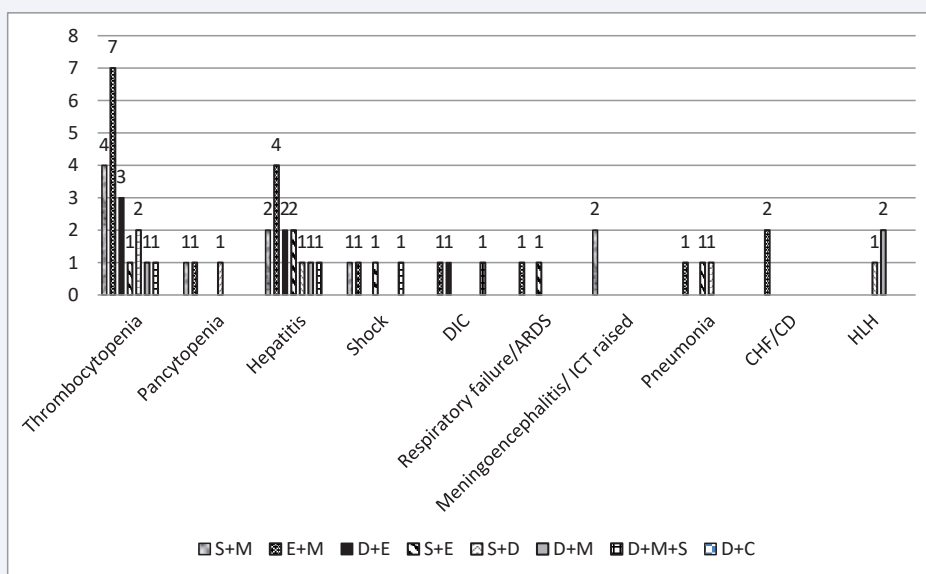


Figure 1 Complications in patients with concurrent Tropical fevers.

AUTHORS' CONTRIBUTIONS

Monika Mtalani and Shyam S Meena designed the study. Monika Matlani, Vinita Dogra, Deepika Meena and Shyam S Meena participated in the data collection and laboratory analysis. Monika Mtalani and Shyam S Meena and Deepika Meena analysed and interpreted the data and wrote the manuscript. Vinita Dogra reviewed and revised the manuscript for intellectual content. All authors read and approved the final version of the manuscript.

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