Publisher
MEDRESEARCH
www.medresearch.in

Tropical Journal of Pathology and Microbiology

2019 Volume 5 Number 8 August

E-ISSN:2456-1487
P-ISSN:2456-9887
RNI:MPENG/2017/70771

Research Article
Illnesses

Prevalence of acute undifferentiated febrile illnesses in a tertiary care centre in Telangana, South India

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DOI: https://doi.org/10.17511/jopm.2019.i08.08

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Introduction: Increased incidence of acute undifferentiated febrile illnesses (AUFI) are observed with the beginning of monsoon season in tropical countries. Diverse aetiologies, overlapping clinical presentations and mixed infections complicate the diagnosis and management of febrile illnesses. Knowledge of the local aetiology and seasonal prevalence of these diseases would enable physicians and policy makers to take adequate control measures. Hence the present study was undertaken to understand the aetiology of AUFI and the prevalence of multiple infections in patients attending our tertiary care hospital in Telangana, South India. **Material and Methods:** A total of 932 patients presenting with AUFI over a period of four months from July to October 2018 were tested for various causes of fever by serological tests. Dengue, scrub typhus, Leptospira and Chikungunya were tested by rapid tests and ELISA. Latex agglutination kits were used for diagnosis of *Salmonella* and *Brucella* infections. Peripheral smear examination was used to diagnose malaria. **Results:** Dengue was the most common infection seen in 21.6% of patients followed by scrub typhus in 9.5%. Peak incidence of Dengue was seen in the month of September and maximum scrub typhus cases were diagnosed in August. Dual infections were documented in 1.9% of patients; most common being dengue with scrub typhus. **Conclusion:** Awareness of the local aetiology of AUFI guides clinicians in prioritising clinical and diagnostic workup and initiating appropriate empirical and supportive therapy. As incidence of multiple infections is increasing, comprehensive clinical and diagnostic exploration for probable pathogens need to be considered in treatment non-responsive AUFI patients.

Keywords: AUFI, Dual infections, Dengue, Scrub typhus, Seasonal prevalence

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How to Cite this Article

M V N L Ram Mohan, VD Teja, Subhada K. Prevalence of acute undifferentiated febrile illnesses in a tertiary care centre in Telangana, South India. Trop J Pathol Microbiol. 2019;5(8):555-561.
Available From https://pathology.medresearch.in/index.php/jopm/article/view/304

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Manuscript Received	Review Round 1	Review Round 2	Review Round 3	Accepted
2019-07-26	2019-08-07	2019-08-10		2019-08-16

Conflict of Interest	Funding	Ethical Approval	Plagiarism X-checker	Note
No	Nil	Yes	5%	

Introduction

Febrile illnesses are very common in the monsoon and post monsoon season in tropical countries. The term acute undifferentiated febrile illness (AUFI) is defined as fever of <14 days duration without any localised source of infection [1]. The common causes of AUFI's are dengue fever, chikungunya, scrub typhus, malaria, Enteric fever, Leptospirosis etc. in the tropical countries [2].

Majority of the AUFI's are arthropod vector borne and disease transmission is influenced by the increased vector density, temperature, humidity, increased growth of vegetation, biting patterns of vectors. Malaria is caused by mosquito-borne *Plasmodium* parasites; *P. vivax* and *P. falciparum*, being responsible for the majority of morbidity and mortality. Dengue and chikungunya are arboviral infections transmitted by the bite of infected *Aedes* mosquitoes. The dengue virus has an incubation of 4–10 days and the disease presentation varies from asymptomatic to severe life threatening complications. Incubation period of Chikungunya ranges from 1 to 12 days following the bite of an infected *Aedes* mosquito. The onset of the disease is characterized by an acute febrile illness, accompanied by rash and severe joint pain that can persist for months [3]. Similar clinical presentation with diverse aetiologies often confounds the diagnosis of febrile illnesses and delays initiation of appropriate treatment.

Infections with multiple organisms further complicate the situation. Malaria is a common co infection in dengue and is an emerging problem across Asian countries [4]. Coinfections of Dengue with Chikun-gunya are predictable as they are transmitted by the same *Aedes* mosquitoes and targeted control measures can potentially reduce the combined disease burden. Scrub typhus is an acute febrile illness caused by the obligate intracellular bacterium *Orientia tsutsugamushi*.

It is transmitted to humans through the bite of the trombiculid mite, which is both the vector and reservoir. Scrub typhus is often under-diagnosed due to nonspecific clinical features and relatively lesser prevalence of the characteristic eschar, making it difficult to differentiate from other febrile illnesses. Dual infections with Dengue and scrub typhus have been reported in the recent past though initially considered to be rare due to the different vectors involved [5].

Limited access to medical care and laboratory diagnostic facilities in developing countries leads to incorrect or delayed diagnosis with consequent morbidity and mortality [6, 7, 8, 9].

Serological tests play a vital role in diagnosis of these febrile illnesses in resource limited settings. Data of the seasonal trend of AUFI's in a region would be useful in ordering relevant diagnostic tests and initiating early appropriate therapy.

The present study was undertaken to find the aetiology of AUFI and the prevalence of multiple infections in patients attending a tertiary care hospital in Telangana, South India.

Materials and Methods

The present study was designed to understand the aetiology of AUFI and the prevalence of mixed infections in patients presenting with febrile illnesses during the monsoon of the year 2018.

Study setting: The present study was conducted in the Department of Microbiology, Nizam's Institute of Medical Sciences, Hyderabad.

Duration: The study was carried out during the monsoon and post monsoon of the year 2018 for a period of four months from July to October.

Type of study: Hospital based cross sectional study.

Sampling method and sample size calculation: Simple random sampling method was used and all in-patients fulfilling the AUFI definition were included.

Inclusion and exclusion criteria: All in-patients with <14 days of fever with no localising source of infection were included in the study.

Patients on immunosuppressive therapy, cancer chemotherapy and HIV infection were excluded.

Data collection procedure: 932 patients with AUFI were tested for Dengue, scrub typhus, Leptospira, Chikungunya, Mycoplasma, Brucella, Enteric fever by serological tests during the study period.

Peripheral blood smear was used to diagnose malaria. Dengue, Leptospira and Scrub typhus were tested by Dengue Duo, Leptospira IgG/IgM and Tsutsugamushi rapid tests respectively (SD Diagnostics).

Scrub typhus IgM ELISA was performed with Scrub typhus *Detect* IgM ELISA (InBios Inc, USA).

Advantage Chikungunya IgM card (J Mitra & Co) was used for diagnosis of Chikungunya. Mycoplasma IgG and IgM ELISA was performed by Calbiotech (USA) kits. Tydal antigen kit (Tulip Diagnostics) was used for performing Widal test.

Latex agglutination (Omega Diagnostics, UK) was used to detect antibodies to *Brucella abortus* and *Brucella melitensis.*

Data analysis: Statistical analysis was performed using the Graph Pad prism statistical software; categorical variables were compared using Fisher' Test. MS Excel 2010 was used to analyse the data.

Ethical consideration: Ethical committee clearance was obtained from Institutional ethics committee and informed written and verbal consent was taken from all the patients.

Results

Sixteen hundred and thirty-five serum samples were received from 932 patients during the study period. 58.4% (545/932) of them were males and 41.5% (387/932) were females with a mean age of 41 years (range 6 to 88 years). Microbiological diagnosis was available in 33.5% (313/932) patients.

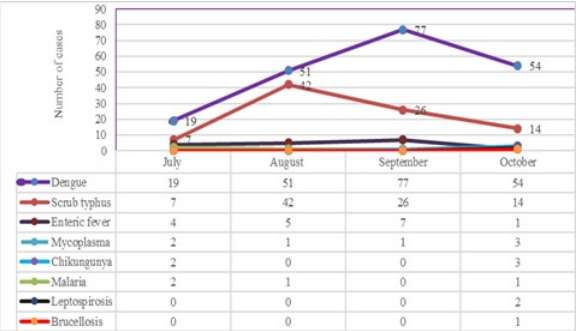
Dengue was the most common infection seen in 21.6% (202/932) of patients followed by scrub typhus in 9.5% (89/932) of patients (Table 1).

Table-1: Prevalence of febrile illnesses

Febrile illness	Number of cases (%)
Dengue	202 (21.6)
Scrub typhus	89 (9.5)
Enteric Fever	17 (1.8)
Mycoplasmosis	7 (0.7)
Chikungunya	5 (0.5)
Malaria	4(0.4)
Leptospirosis	2 (0.2)
Brucellosis	1 (0.1)

Most of the cases of dengue and scrub typhus cases were observed in August; there was a gradual decline of scrub typhus thereafter whereas dengue cases continued to rise till September and slightly tapered off in October (Figure 1).

Figure-1: Seasonal prevalence of undifferentiated fevers

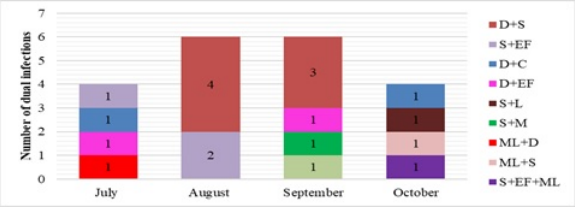


Dual infections were observed in 18 patients (1.9%) and the most common dual infection was Dengue and scrub typhus seen in 7 patients followed by scrub typhus and Enteric fever in 3 patients (Figure 2). Triple infections were observed in 2 patients - scrub typhus, enteric fever and dengue in one patient; scrub typhus, enteric fever with malaria in another patient.

D-Dengue, C- Chikungunya, S-Scrub typhus, M-Mycoplasmosis, L-Leptospirosis, ML-Malaria, EF-Enteric fever

Figure-2: Aetiology of dual infections

Multiple infections were mostly observed in August with four cases of Dengue with scrub typhus and two patients with enteric fever and scrub typhus. One case of triple infection each was seen in September and October-scrub typhus with enteric fever and malaria and scrub typhus with dengue and enteric fever respectively. Scrub typhus was the coexisting illness in 75% (15/20) of patients with multiple infections (Fig 3).



D- Dengue, S- Scrub typhus, C- Chikungunya, EF-Enteric fever, L- Leptospirosis, M- Mycoplasmosis, ML- Malaria

Figure-3: Temporal distribution of dual infections

Discussion

Acute febrile illnesses pose a diagnostic challenge due to their varied aetiology and limited diagnostic capabilities even in tertiary care hospitals. Most of them are caused by arthropod borne viral pathogens followed by bacteria and parasites. Serological tests are useful tools to diagnose these aetiological agents rapidly as they are relatively easy to perform and results can be delivered within a few hours of sample receipt in the laboratory.

The most common cause of AUFI in the present study was Dengue followed by scrub typhus with prevalence rates of 21.6% and 9.5% respectively. Dengue, malaria, scrub typhus, enteric fever and leptospirosis have been identified as major causes of AUFI in Thailand, Malaysia and Nepal [10-14] and a few studies from South India [2, 15, 16].

Dengue was reported to be the major cause of febrile illness from two studies in Dehradun [17] and Rourkela [18]. Scrub typhus is emerging as a major cause of AUFI in South India with one study reporting nearly half of inpatient admissions due to scrub typhus among the AUFI's [3]. Two studies from a south Indian tertiary care hospital in 2007 and 2012-2013 have reported scrub typhus as predominant cause of AUFI-47.5% and 35.9% respectively [2,19]. Another study from Maharashtra in 2015-16 also found scrub typhus to be the predominant cause of AUFI [20].

The prevalence of Enteric fever in the present study was 1.8% compared to 16.5% and 3.7% from two similar studies [17, 19]. Enteric fever cases are expected to rise during the monsoon due to consumption of contaminated water but the apparently lesser prevalence in the present study could be attributed to the fact that the majority of patients access outpatient services for the diagnosis and treatment of enteric fever who were not included in the present study.

A meta analysis and literature review of 43 studies published from 1998 to 2019 to evaluate aetiologies of undifferentiated febrile illness in south and Southeast Asia revealed Dengue as the most common cause of AUFI in 16.6% of patients followed by Scrub typhus (10.7%), malaria (9.8%), Leptospirosis (6.3%) and typhoid (6%) [21].

A multicentre study from six South Indian states in 2011-2012 found malaria to be the predominant cause of AUFI in 17% of patients followed by scrub typhus (16%), bacteraemia (8%), leptospirosis (7%), and Chikungunya (6%) [22]. Relatively low prevalence of malaria (0.4%) was seen in the present study compared reported rates of 0.1% to 12 % from various studies [17, 18, 20, 21, 23]. Rise of non-malarial AUFI's in Asia and Africa has been attributed to the decline of malaria cases in these continents [21, 24].

Peak incidence of scrub typhus was seen in August and maximum dengue cases were observed in September in the present study compared to a study from CMC, Vellore which reported maximum number of scrub and dengue cases in October [19]. In south India, scrub-typhus cases occur mostly in the cooler months (August–January), while in Southeast Asia, scrub-typhus cases are highest in July–November [25].

Mixed infection with more than one organism can result in illness with overlapping symptoms posing diagnostic and therapeutic challenges to the physician [7,26,27,28]. Prevalence of multiple infections in the present study was 1.9% similar to reported rates of 1.88% and 1.3% in two studies [17, 27]. Most common multiple infection was dengue with scrub typhus seen in 7/20 cases as observed in the previous two studies. Dengue with scrub typhus has been reported from two studies from North and South India [29, 30].

Dengue and scrub typhus have many common clinical and laboratory features like rash, hepatic dysfunction and thrombocytopenia and a study from a tertiary care hospital in the south coast of India postulated that normal leukocyte counts, early drop in platelets and hypoalbuminemia could be clues to concurrent scrub typhus infection in Dengue patients [5]. Dengue and Chikungunya co infections have been reported from various states in India [31, 32]. They were seen in only 2/20 patients in the present study though they are thought to be very common as both the diseases are transmitted by *Aedes* mosquitoes.

A microbiological cause of AUFI was determined in only 33.5% of patients in the presnent study. Other causes of AUFI like Japanese encephalitis, Hantavirus, influenza, etc were not explored in the present study due to the financial constraints and limitations in the availability of diagnostic facilities.

Non infectious aetiologies of AUFI could account for a proportion of undiagnosed cases. Rates of determining the aetiologies of AUFI varied from 40% to 73.3% in various studies [13, 33, 34]. A large meta-analysis of 43 studies from 1998 -2019 found that the underlying diagnosis could not be ascertained in 64.6% of patients [21].

Limitations of the study: All the infectious causes of febrile illnesses could not be ascertained due to financial constraints and limited diagnostic capabilities in our hospital.

Conclusion

Awareness of the local and seasonal profile of acute undifferentiated fever is useful to draft logical clinical, diagnostic and treatment algorithms which help the physicians in the correct choice of empirical antibiotics.

This is useful especially for multiple infections coexisting with scrub typhus which respond rapidly to Doxycycline treatment, preventing further compli-cations. Knowledge of the local aetiology of the arthropod borne illnesses aids policy makers to implement appropriate and timely disease and vector control measures.

What the study adds to the existing knowledge?

The present study establishes that Dengue and scrub typhus are the major causes of febrile illnesses during the monsoon in our geographical region.

Empirical treatment of febrile illnesses need to incorporate specific scrub typhus treatment as it coexists in the majority of coinfections and the nonspecific clinical picture precludes the diagnosis. Rising incidence of infections with multiple organisms emphasizes the need for a comprehensive diagnostic workup.

Author contributions

Dr. M. V. N. L. Ram Mohan: Conceptualised the study and prepared the manuscript.

Dr. VD. Teja: Reviewing and editing of the manuscript.

Mrs. K. Subhada: Performed the diagnostic tests and assisted in data analysis and editing of the manuscript.

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