Clinical Spectrum of Acute Undifferentiated Fever - An Experience from a Tertiary Care Centre

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ABSTRACT

Introduction: Region specific awareness about major aetiologies of acute undifferentiated fever (AUF) is important for effective management to reduce morbidity and mortality. Hence, we did a study to know about the aetiology and disease specific clinical profile of acute undifferentiated fever cases in a tertiary care centre in South India.

Material and Methods: A retrospective, observational study was conducted in a tertiary care centre (GIMSR, South India) during June 2018–June 2019. Patients aged 16 years who had a febrile illness for < 21 days, with no localizing signs of infection following initial clinical evaluation were included in the study. Peripheral smear for malarial parasite, Widal test, Dengue rapid NS1 antigen and IgM Combo test, Dengue IgM capture ELISA (MAC-ELISA), Leptospira IgM ELISA, Scrub typhus IgM ELISA, Chikungunya IgM ELISA and blood culture were routinely performed at the hospital.

Results: A total of 248 AUF cases were studied: Dengue (42), Malaria(46), Scrub typhus(27), Scrub typhus with Dengue(7), Chikungunya(11), Enteric fever(37), UTI(26), Leptospirosis(5), Hepatitis A(5), Hepatitis E(5) and Unclear diagnosis(37) were noted.

Conclusion: Malaria, Dengue, Enteric fever and Scrub typhus were the most important major causes of AUF in our study. However, a greater number of undiagnosed cases (37) in our study shows that further research is required in identifying the aetiology of undifferentiated fever.

Keywords: Fever, Acute Undifferentiated Fever, Dengue, Malaria

INTRODUCTION

Infectious diseases are the leading causes of morbidity and mortality in India. Region specific awareness about major aetiologies of acute undifferentiated fever (AUF) is important for effective management to reduce morbidity and mortality. In acute undifferentiated fever (AUF), symptoms are non-specific, and if accurate diagnostic methods are not available, diagnosis remains a challenge to the treating clinician. If diagnostic methods are available, positive results due to subclinical or previous infections and cross reactivity in serological tests, makes interpretation of results a challenge. Awareness of the limitations and strengths of diagnostic tests is necessary in the interpretation of AUF cases.

The main objective of this study was to determine the proportion of AUF caused by malaria, dengue, scrub typhus, chikungunya and leptospirosis among patients admitted.

We conducted this study to evaluate the local prevalence of diseases in this region, clinical presentation of AUF cases to correlate with the symptoms and signs and with specific investigations to make a proper diagnosis and early treatment.

MATERIAL AND METHODS

The study was performed in GITAM Institute of Medical Sciences and Research (GIMSR), Visakhapatnam, Andhra Pradesh, India, a tertiary care centre. Patients aged 16 years or more who had a febrile illness for < 21 days, with no localizing signs of infection following initial clinical evaluation were included in the study, during the period between June 2018 and June 2019. Patients with fever >21 days, with localized focus of infection, autoimmune diseases, connective tissue disorders, HIV, Tuberculosis, hepatitis B and C, vasculitis, leukemia, and malignancy were excluded from the study.

Once the patients were enrolled into the study, data were collected in a prewritten proforma which includes patient's history, clinical examination findings and laboratory

	Frequency	Percent
Male	121	48.7%
Female	127	51.3%
Total	248	100%

Table-1: Gender distribution of AUF cases

	Range	Minimum	Maximum	Mean	Std. Deviation
Age (years)	64	16	80	34.21	11.790
Duration in hospital (days)	12	2	14	4.30	3.064
Duration of Fever in days	20	1	21	7.75	3.610

Table-2:

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investigations. Patients were screened with complete blood picture(CBP),peripheral blood smear for malarial parasite, dengue NS1Ag, IgM ELISA, quantitative buffy coat (QBC) for malaria parasite, serology for dengue, scrub typhus, leptospirosis, Widal test, liver function tests (LFT),renal function tests(RFT), urine routine and a chest radiograph were done in all patients. The blood culture, urine culture, stool culture, ultrasound abdomen, computed tomography scan of Chest and abdomen were done as per indication. ELISA kits were used for HIV, HbsAg, HCV, dengue (NS1 Ag, IgM, IgG,), *Leptospira* (IgM) and Scrub typhus. Rapid tests were done for malaria, dengue, and scrub typhus.

After confirmation of diagnosis, patients were treated with specific treatment for the underlying disease and the rest were treated with supportive treatment. Prior approval was obtained from Ethical Committee of GIMSR and informed consent was obtained by the study participants. Confidentiality of the Patient was maintained.

	Frequency	Percent
Malaria	46	18.5
Dengue	42	16.9
Scrub typhus	27	10.8
Scrub typhus+ dengue	7	2.8
Chikungunya	11	4.4
Enteric fever	37	14.9
UTI	26	10.4
Leptospirosis	5	2
Hepatitis A	5	2
Hepatitis E	5	2
Unclear diagnosis	37	14.9
Total	248	100

Table-3: Distribution of AUF cases according to diagnosis

RESULTS

A total of 248 patients with AUF admitted in GIMSR during June 2018 to June 2019 were studied. In our study, 121 were male and 127 were female patients (Table1). The mean age was 34.2 years with a range of 16-80 years (Table2). As per case definition, malaria positivity was found in

	Malaria (n=46)	Dengue (n=42)	Enteric fever (n=37)	Scrub typhus (n=27)
Age (in Years) (mean)	33.2	32.8	32.4	31.6
Fever duration (in Days) (mean)	4.5	7.6	5.4	5.2
Headache	35(76%)	40 (95%)	21 (56.7%)	15/27
Myalgia	30 (65%)	36 (85.7%)	18 (48.6%)	14/27
Arthralgia	10 (22%)	31 (73.8%)	6 (16.2%)	4/27
Pain abdomen	5 (10.8%)	14 (33.3%)	11 (29.7%)	8/27
Loose stools	5 (10.8%)	11 (26%)	14 (37.8%)	5/27
Retro-orbital pain	4 (8.6%)	17 (40%)	2 (5.4%)	0 (0%)
Oliguria	5 (10.8%)	3 (7%)	0 (0%)	2 (7.4%)
Dyspnoea	0 (0%)	5 (12%)	0 (0%)	4 (14.8%)
Seizures	2 (4.3%)	0 (0%)	0 (0%)	2 (7.4%)
Icterus	12(26%)	8 (19%)	0 (0%)	6 (22.2%)
Lymphadenopathy	0 (0%)	5 (12%)	0 (0%)	5 (18.5%)
Petechiae	0 (0%)	12 (28.5%)	0 (0%)	0 (0%)
Blanching maculopapular rash	0 (0%)	29 (69%)	0 (0%)	0 (0%)
Eschar	0 (0%)	0 (0%)	0 (0%)	14 (51.8%)
Respiratory crepitations	0 (0%)	0 (0%)	0 (0%)	4 (14.8%)
Neck stiffness	0 (0%)	0 (0%)	0 (0%)	2 (7.4%)
Hepatomegaly	14 (30.4%)	16 (38%)	16 (43.2%)	11 (40.7%)
Splenomegaly	28 (60.8%)	10 (23.8%)	12 (32.4%)	7 (26%)
Leucocytosis	10 (21.7%)	0 (0%)	0 (0%)	14 (51.8%)
Leukopenia	0 (0%)	32 (76%)	19 (51.3%)	0 (0%)
Thrombocytopenia	25 (54.3%)	31 (73.8%)	2 (5.4%)	16 (59.2%)
HCT increase > 20%	4 (8.6%)	13 (31%)	2 (5.4%)	2 (7.4%)
Serum creatinine (mg%) > 1.5	13 (28.2%)	11 (26%)	0 (0%)	6 (22.2%)
Serum total bilirubin (mg%)>1.5	24 (52%)	9 (21.4%)	1 (2.7%)	12 (44.4%)
Elevated serum alanine aminotransferase (45–200 U/L)	5 (10.8%)	25 (59.5%)	1 (2.7%)	15 (55.6%)
Ascites	0 (0%)	13 (31%)	0 (0%)	6 (22.2%)
Pleural effusion	0 (0%)	11 (26%)	0 (0%)	3 (11.2%)
Acute kidney injury (AKI)	13 (28.2%)	11 (26%)	0 (0%)	6 (22.2%)
Acute respiratory distress syndrome	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Aseptic meningitis	0 (0%)	0 (0%)	0 (0%)	2 (7.4%)
Overt bleeding manifestations	2 ((4.3%)	2 (4.7%)	0 (0%)	0 (0%)
Shock	2 (4.3%)	0 (0%)	0 (0%)	0 (0%)

Table-4: Disease specific clinical and laboratory profiles of malaria, dengue, enteric fever and scrub typhus

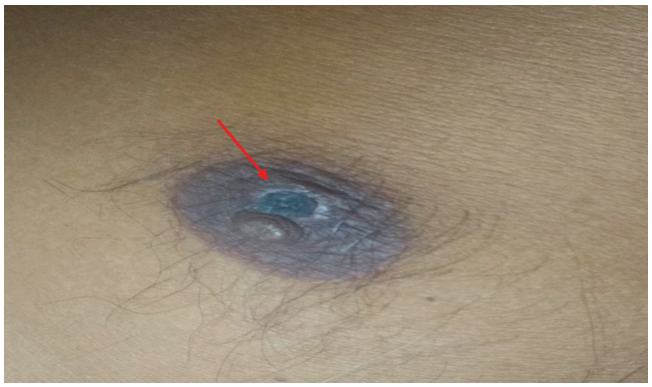

Figure-1: Eschar in scrub typhus

18.5% (46/248), dengue in 16.9% (42/248), scrub typhus in 10.8% (27/248),scrub typhus with dengue in 2.8% (7/248), leptospirosis in 2% (5/248), chikungunya in 4.4% (11/ 248), enteric fever in 14.9% (37/248), UTI (Urinary tract infection) in 10.4% (26/248), Hepatitis A in 2% (5/248), Hepatitis E in 2% (5/248) and unclear diagnosis in 14.9% (37/248) of AUF cases (Table 3). Among malaria cases, 76% (35/46) were Plasmodium vivax, 15.2% (7/46) were P. falciparum and 8.6% (4/46) were mixed vivax and falciparum infection. One case of mixed infection with HEV and enteric fever was noted.

Common complaints associated with febrile illness were non-specific and include myalgia, arthralgia, headache, nausea, vomiting, diarrhoea, malaise, and rash etc.

Many clinical manifestations of malaria, dengue, enteric fever and scrub typhus may closely mimic each other (Table4).

DISCUSSION

Acute undifferentiated fever (AUF) is a common cause of patients seeking healthcare in India.[1,2] Unlike fever of unknown origin (FUO), which has a standard definition, AUF, also known as "acute febrile illness" (AFI) lacks an international consensus definition. As FUO definition requires duration of fever more than three weeks, some authors have defined AUF as fever that resolves within three weeks. Hence, the term AUF is used to denote fevers that typically last less than 3 weeks without any localizing signs and symptoms.[3] The predominance of AUF cases is usually observed during post-monsoon period.

The main objective of our study was to identify and compare the various causes and clinical presentations of acute undifferentiated fever in a tertiary care centre, GIMSR, Visakhapatnam. Most of the patients were in the middle age group (mean age of 34.2). Mean duration of fever was 7.7 days. Both males and females were almost equally affected.

The study revealed the heavy burden of tropical infections such as malaria, dengue, enteric fever and scrub typhus. Previous studies from other regions of India have shown the similar results.[3,4] In our study, the most common cause of AUF is malaria followed by dengue, enteric fever and scrub typhus. Dengue, malaria, scrub typhus, enteric fever and leptospirosis have been identified as major causes of AUF even in other parts of the world.[5,6,7,8] In our study, no definite cause was found in 14.9% of cases and was presumed to be of

viral origin. Further studies are needed to identify the aetiology of fever in unclear diagnosis cases.

Malaria, being diagnosed in 18.9% (46/248) of cases, out of which 14/46 were complicated malaria and the rest were uncomplicated malaria cases. Dengue Fever, being diagnosed in 16.9% of AUF cases. The proportion of dengue fever among all fever cases has been estimated to be 14% in a population-based study in rural South India and 48% in a hospital-based study in urban North India.[9,10] In our study, out of 42 cases, 27 cases were classic dengue fever, 15 cases were dengue haemorrhagic fever and there were no cases of dengue shock syndrome.

In our study, 51.8% patients with scrub typhus were presented with eschar on the body, highlighting the importance of meticulous search for an eschar in AUF cases while eschar was seen only in 40-46% of cases in other Indian studies.[11,12] An eschar (Fig I) is a black adherent scab with a red margin and is painless. It occurs at the site of chigger feeding and is most commonly found in the covered parts of the body.

Mixed infection with more than one aetiological agent can result in an illness with overlapping clinical features resulting in a challenging context for the treating clinician.[13,14] In our study, we observed mixed infection in seven patients with dengue fever and scrub typhus, P. vivax and P. falciparum infection in four patients, and HEV infection and enteric fever in one patient. Although dual infections were indicated by the results of the serology in the present study, the possibility that these apparently multiple infections represent false-positive results, caused by cross-reacting antibodies or non-specific polyclonal immunoreactivity, cannot be excluded.

Enteric fever was diagnosed in 14.9% of AUF cases which is in contrast to only in 4% of cases in Rani et al study.[15] Hepatitis E infection with enteric fever seen in one patient, possibly explained by feco-oral transmission of both infections.

Leptospirosis was diagnosed in 2% of AUF cases in our study which was similar to the study carried out by Joshi et al[3] in which 3 cases were positive among 11 clinically suspected cases.

About seasonal variations for malaria and dengue, the maximum number of seropositive cases were recorded in the post monsoon period. Such seasonal variations have been reported in Arora et al study.[16] Ecological and climate factors influence the seasonal prevalence of both the mosquitos, *A. aegypti* and Anopheles, and *A. aegypti* larval indices are also high during the monsoon and post monsoon period.[17]

Out of 248 patients, 246 patients had a good recovery and 2 patients expired due to septicaemia and multiorgan dysfunction syndrome.

This study helps to initiate empirical treatment for scrub typhus, leptospirosis, or other rickettsial disease, with doxycycline after ruling out malaria and dengue and treating with third generation cephalosporins whenever the enteric fever is the differential diagnosis of the fever in the approach

to treat AUF. This is cost-effective and useful in treating AUF in remote areas of India where advanced investigations are unavailable.

Limitations of the study was viral studies are not done in routine. Detecting a pathogen directly by PCR or culture is more specific than indirect diagnosis by antibody detection. Because of fund constraints, PCR was not used and hence true number of co-infections might have been underestimated. The study is a retrospective analysis and not a prospective one. Community and hospital based well planned prospective studies will give better information about the true incidence, prevalence, and precise aetiologies of AUF. Another limitation in our study was lack of convalescent samples as patients used to get discharged as soon as they became afebrile and many patients did not come for follow up.

CONCLUSION

Malaria, Dengue, Enteric fever and Scrub typhus were the most important major causes of AUF in our study. Meticulous search for an eschar should be done in all AUF cases for early diagnosis of scrub typhus. However, a greater number of undiagnosed cases (37) in our study shows that further research is required in identifying the aetiology of undifferentiated fever. Region specific awareness about aetiologies of AUF would help in timely detection of such cases and hence better management reducing morbidity and mortality in the long run. The findings in our study emphasizes the importance of interpreting diagnostic tests in a clinical context together with symptoms, clinical findings and laboratory tests.

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