Original Article

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Evaluating the Etiology and Disease Specific Clinical Profiles of Acute Undifferentiated Febrile Illness

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Abstract

Background: To evaluate the etiology and disease specific clinical profiles of acute undifferentiated febrile illness (AUFI) in JSS Medical College, Mysore in south India, a tertiary medical center.

Methods: This 2 years prospective, observational study was conducted in JSS Medical College in 150 patients. Clinical evaluation and relevant investigations like Blood culture; malarial parasites and febrile serology (acute and convalescent) were performed.

Results and Observation: A total of 150 AUFI patients were evaluated: scrub typhus (19); malaria (3); enteric fever (2); dengue (11); leptospirosis (19); hantavirus (1), acute bacterial infections (14), HIV (1), hepatitis (1), and unclear diagnoses (79).

Conclusion: This study reports discovery of dengue, typhus fever, leptospirosis, and rare disease like Hanta and more number undiagnosed cases ranging from 15% to 42% in local community. This shows that further research is required in identifying the etiology of undifferentiated fevers.

Key words: Acute undifferentiated febrile illness, Fever, Thrombocytopenia

INTRODUCTION

The acute undifferentiated febrile illness (AUFI) is commonly seen in developing countries especially in tropical regions. The etiology is usually unknown and presents without disease specific focal signs and symptoms. These infectious diseases traverse the most of the boundaries established by medical specialists with multiorgan involvement leading to increased morbidity and mortality in spite of to the availability of newer investigations.

The prevalence of dengue, leptospirosis, malaria, hepatitis, and scrub typhus has reached endemic proportions. With respect to the local prevalence of AUFI patients with hematological complications, if not managed well can become fatal.

A study in a dengue endemic area of Vietnam demonstrated the inability of physicians to accurately diagnose the disease, regardless of their level of training or years of clinical experience.[1] This difficulty was not due to the lack of advanced laboratory equipment. Similar problems are faced by clinicians in the developed world as they struggle to find a specific etiology for AUFI acquired in the tropics. The cause of systemic febrile illness could not be identified by physicians at academic travel medicine clinics in more than half of travelers returning to the United States from South America.[2] In another series, no etiology could be determined in at least one-fourth of hospitalized febrile travelers returning to the United Kingdom from the tropics.[2] Given their similar clinical presentations, many researchers have commented on the difficulty in distinguishing between dengue fever and leptospirosis. In places where dengue is recognized as a significant health problem, leptospirosis may be overlooked as the cause of AUFI, delaying antibiotic administration and leading to increased complications and death.[3]

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Forming guidelines in approach of management with relation to treatment, transfusion and, diagnosis - serology, virology test for AUFI are required to come to a better understanding of the etiology is utmost need. Despite the existence of safe and effective interventions, many people lack access to needed investigations, prevention methods and treatment.

As an average, every 5th or 6th admission in JSS hospital is a case of AUFI. We conducted this study to evaluate the local prevalence, clinical presentation, and seasonal variation of several type of AUFI to correlate with the symptoms and signs and with specific investigations to make a proper diagnosis and early treatment.

METHODS

The study was performed at the medical wards in JSS Medical college hospital, Mysore, Karnataka, India, a tertiary medical care center. Patients who are more than 14 years of age with acute undifferentiated fever with thrombocytopenia of <14 days during the period between July 2009 and July 2011. Patients with fever >14 days, with localized focus of infection in skin, soft tissue, autoimmune diseases, connective tissue, vasculities, idiopathic thrombocytopenic purpura, leukemia, malignancy are excluded from the study.

Once the patients enrolled into the study, a detailed history was elicited and a thorough clinical examination was done. Data were collected in a prewritten proforma; Patients were screened with hemoglobin, total leukocyte count, differential leukocyte count, Platelet count, hematocrit, peripheral blood smear, dengue NS1Ag, IgG ELISA, IgM ELISA, quantitative buffy coat (QBC) for malaria parasite, serology for enteric fever, scrub typhus, leptospirosis, liver function tests (LFT), and a chest radiograph were done in all patients. The blood c/s, urine c/s, ultrasound abdomen, computed tomography scan was done whenever it is indicated. Kits used were from standard diagnostics SD. Elisa kits were used for HIV, HbsAg, dengue (NS1 Ag, IgM, IgG,), *Leptospira* (IgG), rapid tests were done for influenza, hanta virus, weil felix for scrub typhus, QBC and blood picture for malaria, blood culture for widal positive typhoid cases.

In whom a final definite diagnosis was reached, were treated for the disease. Platelet transfusions were done if platelet count was <10,000/cumm or who had bleeding manifestations irrespective of their platelet count. Prior approval was obtained from Ethical Committee of the JSS Medical College Hospital, Mysore and informed consent was obtained by the study participants.

RESULTS AND OBSERVATION

A total number of 150 patients with AUFI admitted to JSS Hospital over 2 years were studied. In our study, 81 were male and 69 were female patients (Figure 1). The mean age was 35.2 years with a range of 16-70 years. Undifferentiated fever was seen in 97 and others with specific etiology were 53. The Malaria was seen in 3, typhoid in 2, typhus in 16, dengue in 8, leptospirosis in 17, hanta in 1, HIV in 1, Hep B in 1, combined illness like Typhus with dengue fever was seen in 2, typhus with leptospirosis was seen in 2, and dengue with leptospirosis was seen in 1 (Table 1).

Clinical manifestation of thrombocytopenia in the form of petechia, hematemesis, malena, menorrhagia, was there in 38 patients, and there was no similar clinical manifestation in the remaining 112 patients. The most common presentation was fever with a headache of 7 days duration which was observed in 46% of the patients. Symptoms

Table 1: Comparison of different studies done in AUFI*

Name of illness	Percentage of points			
	Suttinont study	Stephen study	Anugrha study	shashidhara study
Leptospirosis	36.9	13.2	3	12.6
Scrub typhus	16.0	5.9	47.5	12.6
Viral infection	10.7	-	-	-
Dengue	5.2	5.3	7	7.3
Japanese encephalitis	0.4	1	-	-
Influenza	4.6	-	-	-
Hanta virus	-	-	0.3	0.6
Q fever	0.8	-	-	-
Malaria	-	12.5	17.1	2
HIV	-	-	-	0.6
Hepatitis B	-	-	-	0.6
Enteric fever	-	-	8	1.3
Acute bacterial infection	1.2	-	-	9.3
Unknown	31.7	41	15	52.6

*AUFI: Acute undifferentiated febrile illness

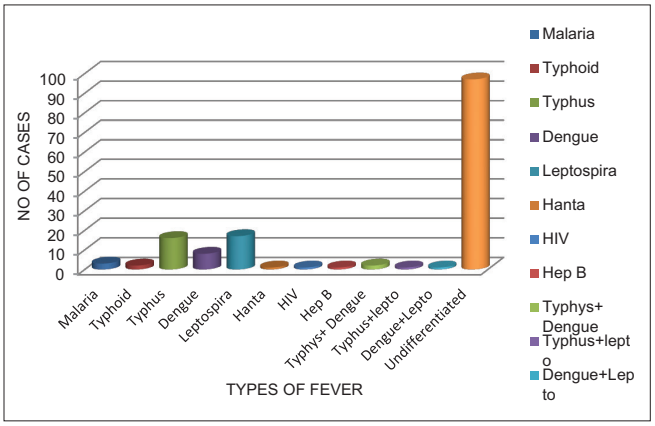

Figure 1: (Different types of fever in our study)

such as Headache, vomiting, lymphadenopathy, skin rashes, hepatospleenomegaly leukopenia, raised LFT were independently associated with scrub typhus. Headache, vomiting, petechia hepatosplenomegaly, leukopenia, raised LFT is associated with leptospirosis. Conjuctival suffusion, abnormal LFT, hepatospleenomegaly was associated with dengue fever. Bleeding manifestation in the form of hemetemisis was seen in one patient.

DISCUSSION

The purpose of this study was to identify the various aetiologies and clinical presentations of AUFI in and around Mysore district in, south India, with the goal of assisting local health professionals in diagnosing, treating, and preventing these diseases.

In our study, the younger and middle-aged patients were more affected as compared to patients above 55 years. Results seen in our study are not unlike those found in other tropical regions of the developing world, although the relative incidence of specific pathogens varies considerably.

In a significant number of cases, thrombocytopenia leads to various bleeding manifestations and influenced the clinical profile of this febrile illness. The mean platelet count at presentation was in the range of 20-30000. In the majority of patients, thrombocytopenia was transient and asymptomatic. Platelet transfusion was given in one patient each in dengue, typhus fever and typhoid fever, 5 in leptospirosis, 15 in undifferentiated fever when platelet count has fallen below 10,000/cumm or patient with bleeding manifestations irrespective of platelet count.

In our study, we observed a combined illness in three patients such as typhus with dengue fever was seen in 2, typhus with leptospirosis was seen in 2, and dengue with leptospirosis was seen in 1. 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. This infers that advanced investigations are essential to isolate the organism and make a proper diagnosis and identify the causative organism.

Out of 150 patients, 146 of them had a good recovery and 4 patients expired due to septicaemia and multiorgan dysfunction syndrome. Sharp decline of platelet counts was noticed during the course of hospital in these 4 cases.

In our study the *Leptospira*, typhus and dengue were common and enteric fever, malaria were less and the proportion of undiagnosed cases were very high but similar when compared to the other studies. Our study showed one positive case of hantavirus which was not commonly observed in our area.

A similar study done by the Anugrahchrispal done in Vellore, Tamilnadu, south India for 1 year observed predominantly scrub typhus and malaria and enteric fever and one case of hanta virus with less no of undiagnosed cases.[4]

A similar study conducted by Suttinont, *et al*. done in five hospitals at different provinces in Thailand.[5] The leptospirosis and rickettsioses, especially scrub typhus, dengue infection or influenza and double infections were thus found to be major causes of AUFI in Thai agricultural workers.

Stephen *et al*. conducted similar study[6] in Ecuadorean Amazon basin, by Viral isolation, reverse transcription-polymerase chain reaction (RT-PCR), along with other investigations and found, predominantly leptospirosis, malaria, rickettsioses, dengue and Q fever, and few cases of brucellosis, Ilhéusencephalitis, and venezuelan equine encephalitis, Oropouche, and St. Louis encephalitis virus infections. None of these pathogens, except for malaria, had previously been detected in the study area. Hence, their presence was unknown to local clinicians and public health authorities. Which once again confirm that advanced investigations are essential to isolate the organism and make a proper diagnosis and identify the causative organism.

The leptospirosis, malaria, scrub typhus, murine typhus, *Rickettsia typhi*, and dengue have been identified as major causes of AUFI in Thailand, Malaysia, and Nepal.[1,6,7] Dengue was found to cause one-third of all cases of acute undifferentiated non-malarial fever in an area of Vietnam.[8] In South America, spotted fever group rickettsia, leptospirosis, and coxiella burneti have been identified as major identifiable causes of AUFI in a subtropical area of northwestern peru.[9] Dengue, malaria, and *Leptospira* were found in AUFI patients in the Amazon basin of Peru.

The above studies have shown leptospirosis, malaria, scrub typhus, murine typhus, *R. typhi*, and dengue were being the major causes of AUFI throughout the world and other illness dependent on the demographic area and its endemicity, vector control and level of hygiene in the area. Stephen study has shown increased no of viral fever and less number of undiagnosed cases as compared to other studies due to special test done like viral isolation or RT-PCR test.

Even when dengue fever and leptospirosis are suspected, currently available rapid serologic tests cannot reliably

detect IgM antibodies until at least the 6th or 7th day of clinical illness thus making it more complex for the treating physician. The advanced investigations such as virus isolation and identification of viral particle are more specific and sensitive. These tests are costly and may give false positive results because of contamination and fail to differentiate between primary or secondary infection. They require advanced laboratories and experts in the concerned field to analyze the tests.

This study helps to initiate empirical treatment for leptospirosis, q fever or other rickettsial disease with doxycycline after ruling out malaria and treating with quinolones or cephalosporin whenever the enteric fever is the differential diagnosis of the fever in the approach to treat AUFI. This is cost-effective and useful in treating AUFI in remote areas of developing countries where advanced investigations are unavailable.

CONCLUSION

Most of AUFI are self-limiting but accurate diagnosis and proper treatment are important in reducing the duration of fever and in preventing potentially lethal complications leading to multiorgan failure.

This study reports for the 1st time a number of important pathogens that have been overlooked in our area. The discovery of dengue, typhus fever and leptospirosis and rare disease like hanta in local community prompted the Local clinical laboratories now offer serologic testing for these diseases. Such testing is admittedly of little utility early in the course of AUFI, but can be useful to establish the etiology during outbreaks and for patients who present after several days of illness.

The type of disease and the incidence also depends on the demographic area and its endemicity, vector control and level of hygiene in the area. With Time clear patterns will emerge, with cumulative experience and advanced investigations, will go a long way to helps us to tackle this problem of undifferentiated fevers head on. It is imperative to maintain a sound epidemiological database of AFIs so that evidence-based diagnostic criteria and treatment guide can be made.

Including our study, the other studies have shown undiagnosed cases ranging from 15% to 42%. This shows that further research is required in identifying the etiology of undifferentiated fevers which are more of viral origin than bacterial.

The drawback of our study is there were less number of cases, and we have not done nucleic acid detection or isolation in cell culture and identification using immunoflorescence.

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