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SURVEILLANCE OF INFECTIOUS ETIOLOGIES AMONG PATIENTS WITH ACUTE FEBRILE ILLNESS IN TELANGANA STATE

Medical Microbiology

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ABSTRACT

Introduction: The worldwide burden of febrile illness, as well as the contribution of several fever-inducing pathogens, have proven difficult to assess, categorize, and quantify. Diagnosing the epidemiology of acute febrile illness is challenging due to lack of specific presentations and lack of diagnosis. **Methodology:** The current investigation was conducted on 135 individuals with acute undifferentiated febrile illness [AUFI]. The serum samples were serologically analyzed using the manufacturer's methods for Dengue & Chikungunya IgM ELISA, Dengue NS1 ELISA, Leptospira IgM ELISA, Scrub typhus IgM ELISA, Q fever IgM ELISA, and Brucella IgM ELISAs. **Results:** Dengue & Chikungunya IgM ELISA, Dengue NS1 ELISA negative samples were processed to identify other zoonotic etiologies, 2/135 of cases [1.4 %] were positive for Scrub typhus IgM ELISA. Further, these 133 samples were processed for other serological assays; 12/133 of the samples [9 %] were diagnosed with Q fever. The remaining 110 samples were processed for Brucella IgM ELISA, which showed 9 [8.1%] positivity. On the other hand, 11 out of 133 [8.2%] and 4 out of 110 [3.6] cases were found to be equivocal for Q fever and Brucella respectively. **Conclusion:** The AUFI case surveillance is necessary as clinically all the AUFI cases present with the same symptoms. Laboratory confirmation is essential to refine disease burden estimates of common causes of AUFI, with the zoonotic infections on the upsurge due to prevailing environmental conditions.

KEYWORDS

Acute undifferentiated febrile illness (AUFI), Scrub typhus, Q fever, Brucella, Enzyme Linked Immunosorbent Assay (ELISA)

INTRODUCTION

The worldwide burden of febrile illness and the contribution of different etiological agents have proven challenging to quantify and classify [1]. Patients with acute undifferentiated febrile illness are difficult to diagnose due to the nonspecific presentation of a wide range of diseases and a lack of appropriate diagnostic tests [2]. Hence, understanding the epidemiology of the causes of fever has essential implications in managing and treating febrile patients. The etiology of acute febrile illness is challenging to differentiate clinically, and laboratory services may be restricted or unavailable in low-resource locations [3]. Moreover, the treating physicians lack information regarding the local epidemiology of causes of severe acute febrile illness, which is necessary to adhere to international management guidelines. Similarly, disease control programs require more data to determine prevention priorities [3].

Dengue, Chikungunya, and malaria infections contribute to a significant proportion of acute febrile illness. However, when screened, many cases remain unidentified and undiagnosed. With the ongoing globalization, landscape disruption, and climate change, these infections often overshadow Zoonoses [9]. It has thus been speculated that present and future generations may face the highest risk of exposure to zoonotic diseases. There has been a lack of an integrated approach to febrile illness. Hence, zoonotic diseases have gone undiagnosed [4].

The current study was conducted to identify the interstices in the understanding of acute febrile illness etiology, a trial was also made to design a road map for diagnosing acute febrile illness, keeping in mind the neglected bacterial zoonoses that can be easily managed with an antibiotic, thereby reducing morbidity and mortality. The data obtained after analysis will facilitate AFI prevention and control measures. Such measures are referred to as the 'One Health' approach, a joint effort by multiple fields of medicine to attain optimal health for humans, animals, and the environment [5].

MATERIALS & METHODS

After Institutional ethical committee clearance, 1088 serum samples from patients of all ages who met the criteria of acute undifferentiated febrile illness [AUFI] were included in the study. 135 out of 748 samples, which were negative and equivocal for Dengue [NS1 & IgM] and Chikungunya [IgM], were randomly selected and screened for other febrile aetiologies (November 2022 to January 2023). Using a structured proforma, data on age, gender, occupation, geographical origin, socioeconomic level, animal contact, and raw milk intake were obtained on the sample day.

A surveillance road plan was created for Acute Febrile illness samples, as detailed below. The serum samples were tested using the manufacturer's instructions [Figure 1].

RESULTS

Serological investigations for Dengue [NS1 & IgM ELISA] & Chikungunya [IgM ELISA] showed 14% and 2.8% positivity. One hundred thirty-five negative samples negative for Dengue & Chikungunya, were randomly selected and screened for other febrile aetiologies by ELISA. Leptospira IgM has revealed zero positivity. Scrub typhus IgM ELISA revealed 1.4% positivity. Q fever ELISA revealed 8.8% positivity while 8.2 % cases were equivocal. Brucella IgM ELISA revealed 6.6% positivity while and 3.6% were equivocal. (Table 1)

Most subjects are in 0-10 age group [42.9%] followed by 21-30 years [29 %]. (Table 2). The Gender distribution among recruited subjects

was more or less equal without much significance. (Table 3). Among Q fever IgM ELISA positives, 50% positivity was seen in Male children aged 0-10 years, whereas 25% positivity was found in females aged 21-30. Overall, the positivity of Q fever was found to be 50%. (Table 4). Among Brucella IgM ELISA positives, 33.3% positivity was seen in Male aged 31-40 years whereas 22.2% positivity was found in females aged 21-30 yrs. Overall positivity of brucella was found to be more in males [66.66%] compared to females [33.3%]. (Table 5).

DISCUSSION

Lack of surveillance and lack of routine diagnostics for acute febrile illness other than Dengue and Chikungunya limits clinical awareness of these diseases. An increased proportion of suspected dengue cases were found to be laboratory-negative. As a result, enhanced acute febrile illness [AUFI] surveillance was initiated in our tertiary care hospital, where a subgroup of samples were randomly selected and processed for other bacterial zoonotic infections such as Leptospira, Scrub typhus, Q fever and Brucella.

In this study, 17% of undifferentiated AUFI patients had positive serology for Scrub typhus, Q fever, and Brucella, which are generally underappreciated once Dengue or Chikungunya ELISAs are negative,11.8% of cases were equivocal for Brucella and Q fever whereas 71% of the cases remained undiagnosed emphasising the need to screen for other etiological agents which are often ignored. Moreira et al reviewed different studies conducted between 2007 and 2016 of AFI case in Latin America and concluded that 49.2 % of people with febrile illness had at least one pathogen. The most frequently reported pathogen was DENV (n = 14), followed by CHIKV (n = 9), ZIKV (n = 7), Leptospira spp. (n = 5), Rickettsia spp. (n = 4) and Hantavirus spp. (n = 3)[6]

In a study conducted by Abhilash et al in South India (2016), a microbiological cause was identified in 82.5% of patients. Scrub typhus was the most common cause of AUFI (35.9%) followed by dengue (30.6%), malaria (10.4%), enteric fever (3.7%), and leptospirosis (0.6%) [7]. Chipwaza et al. researched in Tanzania (2015) with 370 AFI patients aged 2-13 years. Of the 370 persons included, 44 [11.6%] had assumed acute leptospirosis, 26/200 [13%] had proven leptospirosis, and 85 [24.0%] had malaria parasites. Twenty-six people [7.0%] had probable acute brucellosis caused by B. abortus. In contrast, 57 [15.4%] of the recruited people had B. Melitensis [8].

Shrestha et al reviewed 100 studies conducted in South and South-East Asia (2013-2017) and found that the most frequently reported fever aetiology was dengue (reported by 15, 50%), followed by leptospirosis (eight, 27%), scrub typhus (seven, 23%) and Salmonella serovar Typhi (six, 20%).[9]

A study conducted by Gowri Veligandla et al in CMC, Vellore (2017) concluded that Typhoid was the leading cause of AUFI 28(24.14%), followed by Dengue 12(10.35%), Malaria 6(5.17%) and Scrub typhus 2(1.72%). However, 5(4.31%) cases had Mixed infections. There were almost 63(54.31%) undiagnosed infections[10].

In a study by Bhatia et al. (2022) in Uttarakhand, India, out of fifty-three, Dengue and Typhoid IgM positivity was observed in two and eight patients, respectively. Six and five patients were tested positive by Leptospira and scrub typhus IgM ELISA, respectively [11]. Study conducted in Punjab by Singh et al. reported 10 leptospirosis and nine scrub typhus positives out of 270 patients screened [12].

There are limited studies conducted in India on AUFI surveillance. Different studies conducted worldwide have chosen different pathogens as etiological agents for AUFI cases depending on their geographical area though most of the studies included Dengue, Chikungunya, Malaria, Salmonella Typhi, Scrub typhus and Leptospira. In the present study, Leptospira and Scrub typhus included had a positivity of 1.4 % but to our surprise, our results showed a positivity of 10.3% for Q fever and Brucella together which were expected to have a lower positivity and more over 11.1 % of the cases were also equivocal for Q fever and Brucella. These findings suggest us that there is now increased risk of zoonotic diseases due to urbanization and destruction of natural habitats and these diseases should also be given importance in the diagnosis of AUFI cases.

Hence, there is a need to customize the etiological agents to be included in AUFI diagnostic algorithms taking into consideration the geographical area, vectors, animals and occupation of the people and other important epidemiological factors. Base line data of other febrile illness etiological agents is also essential to know the prevalence and incidence of diseases which will help us in deciding which panel of tests to be done and what further interventions to be carried out.

The burden of various diseases has been underappreciated. Early diagnosis and prompt treatment can significantly reduce complications and mortality. Establishing good surveillance and instituting appropriate control measures are urgently needed. The lack of knowledge about the specific etiologies comprising the differential diagnosis of dengue and chikungunya hinders our ability to make correct diagnoses, to administer appropriate treatment, and to implement effective public health interventions.

CONCLUSION

AUFI case surveillance is required since clinical diagnosis alone cannot catch all febrile patients. Laboratory confirmation is essential to refine disease burden estimates of common causes of AUFI. With the zoonotic infections on the upsurge due to prevailing environmental conditions, these should also be a part of the algorithms without underestimating their burden. Once epidemiologic databases of various etiologies have been discovered based on geography, creating a road map for case identification will aid in providing the best healthcare service and anticipating pandemic preparation.

Limitations

The study's limitations include the small study group recruited, which may not be representative of the causes of fever in the general population, the use of ELISA for infection confirmation, the processing of the negative sample from the previous step for the next step, and the possibility that co-infections were missed in a few cases. A further limitation of the study was that it only looked at a few infections and did not investigate all possible causes of fever.

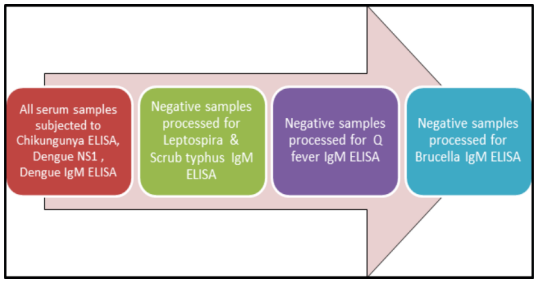

Figure 1: A Surveillance Road Plan For Acute Febrile Illness.

Table 1: Serological Investigations Of AUFI Samples (n=1088)

Name of the test done	Total Samples screened	Positives	Equivocal	Negatives
Dengue NS1 ELISA	1088	36 (3.3%)	3 (0.27%)	1049 (96.4%)
Dengue IgM ELISA	1088	119 (10.9%)	79 (7.2%)	890 (81.8%)
Chikungunya IgM	1088	31 (2.8%)	72 (6.6%)	985 (19.5%)
Leptospira IgM ELISA	135	0	0	135 (100%)
Scrub typhus IgM ELISA	135	2 (1.48%)	0	133 (98.5%)
Q fever IgM ELISA	133	12 (8.8%)	11 (8.1%)	110 (81.4%)
Brucella IgM ELISA	110	9 (6.6%)	4 (2.96%)	97 (71.8%)

Table 2: Age-wise Distribution Of Subjects [n=135]

Age in years	Total subjects [%]
0-10 yrs	58 (42.9%)
11-20 yrs	14 (10.3%)
21-30 yrs	29 (21.5%)
31-40 yrs	18 (13.3.%)
41-50 yrs	7 (5.18%)
51-60 yrs	7 (5.18%)
61-70 yrs	2 (1.4%)
Total	135

Table 3: Gender Base Distribution Of Subjects [n=135]

Age	Male [%]	Female	Total subjects
0-10 yrs	39 (28.1%)	19 (14.7%)	58(42.9%)

11-20 yrs	5 (3.7%)	9 (6.6%)	14 (10.3%)
21-30 yrs	10 (7.4%)	19 (14.07%)	29 (21.4%)
31-40 yrs	10 (7.4%)	8 (5.9%)	18 (13.3%)
41-50 yrs	5 (3.7%)	2 (1.48%)	7 (5.18%)
51-60 yrs	2 (1.48%)	5 (3.7%)	7 (5.18%)
61-70 yrs	0 (0%)	2 (1.48%)	2 (1.48%)
Total	71 (52.59%)	64 (47.4%)	135

Table 4: Q Fever IgM ELISA Positive Data [n=12]

Age	Male	Female	Total
0-10 yrs	6 (50%)	1 (8.3%)	7 (58.3%)
11-20 yrs	0	0	0
21-30 yrs	0	3 (25%)	3 (25.0%)
31-40 yrs	0	1 (8.3%)	1 (8.3%)
41-50 yrs	0	0	0
51-60 yrs	0	1 (8.3%)	1 (8.3%)
Total	6 (50%)	6 (50%)	12 (100%)

Table 5: Brucella IgM ELISA Positive Data [n=9]

Age	Male	Female	Total
0-10 yrs	1 (11.1%)	1 (11.1%)	2 (22.2%)
11-20 yrs	0	0	0
21-30 yrs	1(11.1%)	2 (22.2%)	3 (33.3%)
31-40 yrs	3 (33.3%)	0	3 (33.3%)
41-50 yrs	1 (11.1%)	0	1 (11.1%)
Total	6 (66.66%)	3 (33.3%)	9 (100%)

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