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Acute undifferentiated fever in children: Clinical and Etiological profile

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Abstract

Introduction: Acute febrile illness (AFI) is defined as a patient with fever of 38°C or higher at presentation or history of fever that persisted for 2-14 days with no localizing source. Fever is the main clinical symptom of various tropical infectious diseases [1].

Materials and Methods: This is a Prospective and observational study was conducted at Paediatric Department, Gayatri Vidya Parishad Institute of Health Care and Medical Technology over a period of 1 year. Acute febrile illness (AFI) is defined as a patient with fever of 38°C or higher at presentation or history of fever that persisted for 2-14 days with no localizing source. Details of history and results of a thorough physical examination were entered on a standard data collection sheet.The routine baseline investigations included complete blood count analysis, serum electrolytes, liver and renal function tests.

Result: In this study typhoid fever was the most common cause of undifferentiated fever (28.3%) followed by malaria (21.6%), dengue fever (19.1%), Acute gastroenteritis (14.1%), Pneumonia (9.1%), Bronchiolitis (5.0%), Hepatitis (1.6%) and Pharyngotonsillitis (0.8%%). Treatment-Enteric fever was treated with Ceftriaxone. Chloroquine was used for treatment of Malaria. Dengue was treated symptomatically and with fluids according to Dengue protocol. If fever persisted even after 6 days of antibiotics, then Azithromycin was added. In the undiagnosed fever category, received empirical antibiotics.

Conclusion: A high prevalence of Typhoid, malaria and dengue in this study. The overlap probably reflects an undefined level of previous infections, cross reactivity and subclinical infections in the population, rather than high prevalence of coinfections.

Keywords: Acute febrile illness, short febrile illness, acute fever

Introduction

Unlike fever of unknown origin (FUO), which enjoys a standard definition, acute undifferentiated fever (AUF), also known as “acute febrile illness”, “short febrile illness” or “acute fever” lacks an international consensus definition [1]. In acute undifferentiated fever (AUF), symptoms are unspecific and if accurate diagnostic methods are not available, empirical treatment needs to be broad in order to avoid deaths. Prevalence data and access to affordable, sensitive and specific diagnostic methods are tools to provide targeted and effective treatment of severe acute infections, and to avoid further development of antimicrobial resistance in India [2].

A variety of etiologies have been reported in patients presenting with acute undifferentiated fever in tropical areas. Malaria, dengue fever, scrub typhus, other rickettsioses, leptospirosis, and enteric fever are common causes of acute undifferentiated fever, causing considerable morbidity, mortality, and economic burden [3]. However, the etiologic spectrum of acute undifferentiated fever has been poorly characterized in non-tropical areas [4].

Diagnosis of many etiologies of AUF in the tropics can be established with help of simple tests, such as peripheral smear examination or rapid diagnostic tests (RDTs) for malaria or

dengue. [5]. Some other etiologies need more sophisticated tests such as ELISA for rickettsial infections, MAT or ELISA for leptospirosis or PCR based tests for paramyxoviruses [6].
However, multiple positive diagnostic test results in the same patient are common. Positive tests 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 both in the interpretation of epidemiological surveys and when approaching the individual fever patient [7].

Materials and Methods

This is a Prospective and observational study was conducted at Paediatric Department, Gayatri Vidya Parishad Institute of Health Care and Medical Technology over a period of 1 year.

Inclusion criteria: All the patients who were admitted in the ward or intensive care unit with complications of acute febrile diseases, patients 6 months to 14 years of age were included in the study.

Exclusion criteria: Patients with associated infections when the complications cannot be attributed to febrile illness or patients with haematological malignancies, autoimmune disordersand those on immunosuppressant were excluded from the study.

Case definition

Acute febrile illness (AFI) is defined as a patient with fever of 38°C or higher at presentation or history of fever that persisted for 2-14 days with no localizing source. Details of history and results of a thorough physical examination were entered on a standard data collection sheet. The routine baseline investigations included complete blood count analysis, serum electrolytes, liver and renal function tests.
Malaria blood smears, Scrub typhus IgM ELISA, *Leptospira* IgM ELISA, Chikungunya IgM ELISA, Dengue rapid NS1 antigen and IgM/IgG Combo test and blood cultures. In order to improve detection of IgM antibodies serological testing was delayed until five days of fever, if possible. Blood was cultured with conventional methods or automated and if growth was detected, the isolate was identified at each site and frozen, then in Transport swab sent to the reference laboratory for re-identification and confirmation.
The following investigations were performed at the reference laboratory at CMC: Scrub typhus IgM ELISA, *Leptospira* IgM ELISA, Chikungunya IgM ELISA and Dengue NS1/IgM Combo test, only if not performed at local site. Dengue IgM capture ELISA was performed at reference laboratory on all samples. Scrub typhus immunofluorescence (IFA) was performed on all IgM ELISA positives and some ELISA negatives. *Leptospira* Microscopic Agglutination Test (MAT) was performed on all IgM ELISA positives and some ELISA negatives. The immunochromatographic malaria rapid diagnostic test (RDT) was performed on all samples.

Results

In present study, a total of 120 patients with acute undifferentiated fever were evaluated out of these 83 (59.2%) were male and 83 (59.2%) were female (table-1).

Table 1: Distribution of gender

Gender	No. of patients	Percentage
Male	83	59.3
Female	57	40.7
Total	120	100

Table 2: Distribution of different age groups of patients

Age	No. of patients	Percentage
<4 years	31	25.8
5-10 years	46	38.4
11-14 years	43	35.8
Total	290	100

In table 2, in our study, the most of the patients the age group of 5-10 years i.e., 46 out of 120 (25.8%), followed by 11-14 years, i.e., 43 out of 120 (35.8%).

Table 3: Clinical Symptoms and sign

Clinical Symptoms and sign	No. of patients	Percentage
Pyrexia	120	100
Cough and Cold	112	93.3
Abdominal Pain	93	77.5
Diarrhoea	73	60.8
Vomiting	46	38.3
Headache	22	22.5
Hepatomegaly	2	5.8
Splenomegaly	1	0.8

In table-3, out of 120 patients, most common symptom was pyrexia (100%), Cough and Cold (93.3%), Abdominal Pain (77.5%), Diarrhoea (60.8%), vomiting (38.3%), headache (18.3%), (46.8%), hepatomegaly (5.8%) and splenomegaly (0.8%).

Table 4: Acute febrile illness aetiology

Final aetiology	No. of patients	Percentage
Typhoid	34	28.3
Malaria	26	21.6
Dengue	23	19.1
Acute Gastroenteritis	17	14.1
Pneumonia	11	9.1
Bronchiolitis	6	5.0
Hepatitis	2	1.6
Pharyngotonsillitis	1	0.8

In table 4, in this study typhoid fever was the most common cause of undifferentiated fever(28.3%) followed by malaria (21.6%), dengue fever (19.1%), Acute gastroenteritis (14.1%), Pneumonia (9.1%), Bronchiolitis (5.0%), Hepatitis (1.6%) and Pharyngotonsillitis (0.8%).

Table 5: Treatment of Acute Undifferentiated fever in children

Final aetiology	No. of patients	Percentage
Ceftriaxone	59	49.1
Chloroquine	26	21.6
Doxycycline only	21	17.5
Ceftriaxone or Azithromycin	19	15.8
Doxycycline or Azithromycin	17	14.1

In table 5, treatment-Enteric fever was treated with Ceftriaxone. Chloroquine was used for treatment of Malaria. Dengue was treated symptomatically and with fluids according to Dengue protocol. If fever persisted even after 6 days of antibiotics, then Azithromycin was added. In the undiagnosed fever category, received empirical antibiotics.

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Discussion

AUF poses a diagnostic and therapeutic challenge to the health workers, particularly in limited resource settings. A number of viruses, bacteria, protozoa and rickettsia can cause FUO. The non-specificity of symptoms and signs and lack of availability of accurate diagnostics not only test the clinical mettle of even astute physicians but often leads to irrational use of antibiotics and antimalarials [8]. Some fever syndromes have a clearer localization to skin and soft tissue (abscess or cellulitis), meninges or neural tissue (headache, neck-stiffness, altered sensorium with or without focal neurological signs), respiratory tract (cough, breathlessness), or urinary tract (dysuria, hematuria) [9].These syndromes have better developed guidelines for their management. On the other hand, AUF-syndromes (such as fever-rash, fever-myalgia, fever arthralgia, fever-hemorrhage and fever-jaundice) have overlapping etiologies, which makes their diagnosis and management even more challenging [10].

Fevers with proven diagnoses are known as diagnosed-AUFs; those that defy diagnosis are called undiagnosed undifferentiated fevers (UUF) [11]. Because malaria is an important and treatable cause of AUFs in the tropics and ranks number one in the differential diagnosis of acute fevers, patients who test negative for malaria are assigned a diagnosis of non-malarial AUFs [12]. Many UUFs often resolve either on their own or in response to empiric therapies. Those AUFs which persist and total duration of illness becomes longer than three weeks are classified as FUO [13].

History and physical examination, the traditional tools used by health workers, worldwide, can provide important clues for the etiology of AUF. And yet, symptoms and physical signs lack accuracy and precision to rule in or rule out a specific infectious disease causing AUF[14]. Unfortunately neither history nor physical examination is accurate enough to distinguish the etiologies of acute undifferentiated fevers. For example, a third of patients with dengue present with cough, nasal stuffiness or sore throat-symptoms traditionally associated with upper respiratory infections. An enlarged liver and spleen could be found in malaria, dengue, typhoid fever and leptospirosis. Similarly, headache, neck stiffness and other signs of meningeal inflammation are traditionally associated with meningitis, but these signs lack accuracy for ruling in or ruling out meningitis[15].

The warning signs of severe dengue (severe abdominal pain or tenderness, persistent vomiting, lethargy or restlessness, abrupt change from fever to hypothermia, bleeding, pallor, cold/clammy extremities, liver enlargement on physical exam, or abnormal mental status) are noted in a minority of patients with severe dengue and in most cases, develop less than one day prior to hospitalization [16].

Indeed, empirical treatment with doxycycline or azithromycin in patients with non-malarial acute undifferentiated fevers might be a clinically apt strategy for reducing morbidity and mortality [17]. Both the drugs have a comparable efficacy against salmonella, rickettsial organisms as well as leptospirosis [18]. In a study in Thailand, 296 patients with AUF (23% with leptospirosis, 19% with scrub typhus, 5% with murine typhus, 4% with *Leptospira* and scrub typhus dual infection and 50% without a specific diagnosis) were randomized to either a three- day oral azithromycin or a seven- day oral doxycycline. Fever vanished equally quickly in both groups, but patients receiving oral doxycycline tended to have more frequent adverse events [19].

In a meta-analysis of 17 randomized controlled trials evaluating various drug treatments in management of scrub-typhus, doxycycline and azithromycin were comparable in reducing the symptom duration and resolution of fever; however doxycycline yielded more adverse effects than azithromycin [20]. Fluoroquinolones should not be used for management of scrub typhus due to presence of gyrase a mutation in the organism [21]. In a meta-analysis comparing various drug therapies for enteric fever, azithromycin was found to be not only as good as cephalosporins for cure rates but was superior with respect to relapse rates. While efficacy of azithromycin based regimens is well established in adults, its utility in children remains to be demonstrated [22]. Penicillins as well as doxycycline have been used in management of leptospirosis [23]. Antibiotics other than penicillin were found to be as good or even better in a

recent meta-analysis [24].

Conclusion

A high prevalence of Typhoid, malaria and dengue in this study. The overlap probably reflects an undefined level of previous infections, cross reactivity and subclinical infections in the population, rather than high prevalence of coinfections.

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