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Original Research Article

Fever in the tropics: aetiology and clinical profile of fever of unknown origin in children-a prospective observational study in a tertiary care hospital in South India

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ABSTRACT

Background: Fever of unknown origin (FUO) is an important cause of morbidity and mortality in children, especially in tropical countries with varied aetiology and clinical presentation. Aim of this study is to determine the aetiology and outcome of FUO in Indian children. Study design is Prospective, observational study.
Methods: We enrolled 75 children aged 1 to 12 years who were admitted with fever >8 days to the paediatric department from January 2015 to August 2016. Initial evaluation included complete blood count, peripheral smear, urine analysis, chest radiography, blood culture and tuberculin test.
Results: In 72 children (96%), a definitive diagnosis could be established, whereas 3 children (4%) remained undiagnosed. Most common aetiology of FUO was infectious disease (90.6%) followed by malignancy (4%) and collagen vascular disease (1.3%). Among the infections group, scrub typhus was found to be the commonest aetiology (52%).
Conclusions: Infections were the most common etiological factor for FUO in children aged 1-12 years of our region.

Keywords: Etiology, Fever of unknown origin, Infectious Disease, Scrub Typhus

INTRODUCTION

Fever is the chief complaint in up to one third of patients presenting to pediatricians.[1,2] FUO represents a prolonged febrile illness without an established etiology despite thorough evaluation. A consensus definition for FUO is lacking in children as different studies have used different definitions, thus preventing meaningful comparisons and firm conclusions regarding the etiology of FUO. The etiology of FUO in a given population varies with geographical and socio-economic factors, age distribution, sex difference, time of study, local disease patterns and epidemiology.[3] It is difficult to compare studies of FUO in developed countries with those from resource-poor settings where there is limited availability of expensive serological and other tests.

While the paediatric literature on FUO is limited, studies on Indian children are even fewer. Therefore, this present study was conducted to investigate the etiology of FUO in children reporting to a tertiary care hospital in the south India, using the most commonly accepted clinical definition of FUO. This knowledge will help in formulation of regional guidelines for effective management of such children.

METHODS

This prospective observational study was conducted in tertiary care hospital in south india, from January 2015

and August 2016. The study was approved by the institute ethics committee. Informed consent was taken from the parents prior to inclusion of individual into the study.

The primary objective was to determine the etiology and outcome of FUO. The secondary objectives were to correlate the clinical profile with the etiological factor and to ascertain whether the etiology can be identified in all cases with the available laboratory work up.

Study definitions

FUO was defined as fever of at least 8 days duration in children with no apparent diagnosis with the initial workup in the hospital or as an outpatient.[4] This is the most accepted clinical definition of FUO in children.

Inclusion and exclusion criteria

All Children of 1-12 years of age, presenting to the pediatric emergency or outpatient department with fever more than or equal to 8 days duration were included.[4] Children with diagnosed immunocompromised states and children on treatment with immunosuppressive medications were excluded.

Procedure

A detailed history was taken from the patients, including the history of travel. After history, detailed general and systemic examinations were performed, which was repeated on daily basis to look for any evidence of underlying etiology. Clinical and biochemical data were recorded on a structured proforma. Initial investigations included complete blood count with erythrocyte sedimentation rate, peripheral blood smear, complete urine analysis, routine biochemistry, chest radiography and urine/stool/blood culture. Further diagnostic tests include, serological tests for bacteria and virus, tuberculin skin test, immunological markers like ANA, C3, C4, C-ANCA, HIV, abdominal/lymph node USG, Contrast CT or MRI, echocardiography etc. was done as and when needed. They were based on the results of initial tests or clue from daily examination. More invasive investigation including lumbar puncture, pleural, ascitic fluid analysis, lymph node aspiration or excision, bone marrow aspiration, biopsy and culture or liver biopsy were done if indicated. Children were classified into four categories of FUO, (5) viz. infections, malignancy, autoimmune and undiagnosed. Statistical analysis was carried out using SPSS version 19.0 (IBM SPSS, US) software Chi- square test of significance was used to assess the correlation between pairs of categorical variables. A p-value <0.05 was considered as significant.

RESULTS

A total of 75 children fulfilled the study criteria for FUO. The male: female ratio was 1.4:1. The median age was 6 years (range 1 to 12 y). Thirty four (45.3%) children were aged 1 to 5 years and 41 (54.7%) were aged 5 to 12 years old. The mean duration of fever was 10.5 days (range 8-27). Clinical characteristics are illustrated in Table 1.

Table 1: Characteristic of 75 children admitted with fever to a tertiary care hospital in south India from January 2015 to August 2016.

Characteristics	Patients (n=75)
Age (years)	
Mean (median, range)	7.2 (6, 1- 12)
Gender	
Male (n)	44
Female (n)	31
Fever duration (days)	
Mean (median, range)	10.5 (9.2, 8-27)
8-14 days (n)	72
>14 days (n)	3
Length of stay (days)	
Mean (median, range)	5.3 (4.5, 3-32)

The associated clinical features are summarized in Table 2. The patients with infectious disease tended to have chills/rigors, myalgia, vomiting and poor appetite and reduced activity. Pallor, lymphadenopathy and splenomegaly were predominantly seen in patients with scrub typhus and malignancy as a cause of FUO.

A definitive diagnosis was established in 72 (96%) children after thorough investigations. No diagnosis was made in the remaining 3 (4%). Out of 72 cases with diagnosis, infections were the most common cause of FUO (94.4%), followed by malignancies (4.2%) and autoimmune disorder (1.4%) (Table3).

Infections caused by Rickettsial pathogens dominated the group with (52%) followed by bacterial (38%), viral (6%) and protozoan (4%) pathogens. The most common cause was scrub typhus which was seen in 35 of 68 (52%) patients in the infectious group. Enteric fever (13%), pneumonia (7%) and urinary tract infection (7%) were the predominant bacterial infections seen in this study. Malaria was reported in 3 (4%) cases based on Rapid malarial card test (LDH based card tests) and thin & thick smear analysis by a trained microbiologist (2 cases of plasmodium vivax and 1 case of plasmodium falciparum). Our region is not endemic for malaria and not surprisingly all the 3 children with malaria had a history of recent travel to endemic areas. Hepatitis A infection was the commonest viral infection presenting as FUO (6 % of cases). Only 2 children had tuberculous lymphadenitis.

One of the malignant diseases causing FUO, acute leukemia (2 children) was the most common followed by Neuroblastoma (1 child). One child was diagnosed to have systemic lupus erythematosus based on presence of both anti-dsDNA and anti-nuclear antibodies.

Table 2: The association of clinical findings with cause of fever of unknown origin (FUO).

Associated clinical findings	Infectious disease (n = 68)	Malignancies (n = 3)	Autoimmune (n = 1)	Undiagnosed (n = 3)
Chills and rigor	38 (55.9%)	2 (66.7%)	1 (100%)	2 (66.7%)
Myalgia	27 (39.7%)	1 (33.3%)	0 (0%)	1 (33.3%)
Vomiting	22 (32.4%)	1 (33.3%)	0 (0%)	1 (33.3%)
Poor appetite and activity	22 (32.4%)	1 (33.3%)	0 (0%)	1 (33.3%)
Pallor	42 (61.8%)	2 (66.7%)	1 (100%)	2 (66.7%)
Lymphadenopathy	39 (57.4%)	2 (66.7%)	0 (0%)	2 (66.7%)
Rash	10 (14.7%)	0 (0%)	1 (100%)	0 (0%)
Splenomegaly	56 (82.4%)	3 (100%)	1 (100%)	2 (66.7%)

Table 3: Final identified causes of fever of unknown origin in children.

Etiology	Diagnosis	No. (%)
Infectious disease (68)	**Bacterial (26)**	
	Enteric fever	9 (13%)
	Pneumonia	5 (7%)
	UTI	5 (7%)
	Sepsis	4 (6%)
	TB lymphadenitis	2 (3%)
	Abdominal wall abscess	1 (2%)
	Viral (4)	
	Hepatitis A	4 (6%)
	Rickettsial (35)	
	Scrub typhus	35 (52%)
	Parasitic (3)	
	Malaria	3 (4%)
Malignancy (3)	Acute lymphoblastic leukemia	1 (33%)
	Acute myelogenous leukemia	1 (33%)
	Neuroblastoma	1 (33%)
Autoimmune disease (1)	SLE	1 (100%)
Undiagnosed		3
Total		75

Table 4 illustrates the diagnostic yield of various tests performed in the study. The clinical suspicion of Tuberculosis remains high thereby resulting in chest X ray and Mantoux being done for most of the children with prolonged fever. But as is evident from the study, the diagnostic yield is low.

All the patients, were diagnosed, treated and discharged successfully with no mortality.

DISCUSSION

This prospective, observational study shows that infections are the most common etiological factor for FUO in children from 1 year to 12 years of age in this region of South India. Scrub (Rickettsial) typhus is the leading cause of the infections presenting as FUO. Various retrospective studies done previously on the evaluation of FUO have also demonstrated that infections are the most common cause of FUO. This finding is also in accordance to studies done by Joshi et al, in Indian children and Kejriwal et al, in Indian adults. In this study, the most common infectious cause of FUO was Rickettsial infection in contrast to the other reported Indian studies which found that tuberculosis and enteric fever were the most common etiologies.[6,7] The geographical variation could explain the differences in the etiology. In a recent systemic review analyzed by Amy Chow et al, comparing data between developed and developing nations concluded that infection is consistently the most common cause of FUO in children but the type of infections vary.[4] Also, in studies by Cruz et al, Ciftci et al, and Joshi et al, malignancy contributed more than collagen vascular diseases to the causes of FUO.[7-9] In decreasing order of frequency, the three most common causes of FUO identified are infectious diseases, connective tissue diseases and malignancy.[2,10-18]

This is the first attempt for a reasonably large prospective study of FUO in Indian children using the recent definition of FUO i.e. fever of more than or equal to 8 days duration. We have been able to establish a specific etiological diagnosis for FUO in 96% of cases.

Scrub typhus has been reported as an emerging infectious disease for the last 5 decades in this country.[19,20] In recent years, the high prevalence of Scrub typhus has also been noticed in South India. Our study also supports this fact. It is necessary to evaluate the epidemiology and clinical profile of Scrub typhus in large population based studies.

The traditional way of clinical diagnosis of scrub typhus was by detection of eschar and rashes with a history of outdoor activity. In the present study, only 16 children (45%) of the cases with scrub typhus presented with eschar. This is comparable with studies done in South Vietnam and Taiwan, where eschar was documented in

46%, and 60% of the patients respectively. In most of the Indian studies, eschar was reported only in very few patients and this may be because usually, the eschar goes unnoticed in dark skinned individuals. The Gold standard test for diagnosis of scrub typhus is immune fluorescence antibody test (IFA) but IFA test is technically very demanding, subjective, needs an experienced observer and not commonly available in India. ELISA on the contrary is simple, easy interpret, can be performed in laboratories and fairly comparable with IFA in terms of sensitivity and specificity.

In this study, 29 children were diagnosed both on clinical and serological studies based on IgM ELISA; and 6 were diagnosed based on the presence of eschar and other clinical symptoms and signs like myalgia, lymphadenopathy and hepatomegaly. In all children with Scrub typhus, an excellent and immediate response (dereference of fever within 48 hours) was observed to specific antibiotic treatment with either Azithromycin or Doxycycline. Among the 35 children with scrub typhus as a cause of FUO, only four had complications- three in the form of scrub typhus meningo-encephalitis and one had migratory polyarthritis. All these children had these complications at presentation. None of them deteriorated after treatment or during hospitalization. Thus, it underlines the fact that early diagnosis and timely antimicrobial therapy prevents complications in children with scrub typhus.[21]

Table 4: Use of diagnostic procedures among 75 patients admitted with fever to a tertiary care hospital in south India.

Diagnostic procedure	Patients tested	Diagnostic yield* N %	
Chest X ray	75	5/75	6.7
MRI	5	1/5	20
Abdominal USG	25	1/25	4
CT	2	0/2	0
HBsAg detection	4	0/4	0
IgM HAV	4	4/4	100
Scrub typhus IgM ELISA	60	35/60	58.3
Widal	70	9/70	12.9
Rapid malarial card test (LDH based card tests)	25	3/25	12
Malarial microscopy	40	3/40	7.5
Tuberculin test	70	1/70	1.4
Blood culture	75	7/75	9.3
Urine culture	30	5/30	16.7
CSF culture	8	0/8	0

In this study, the second most common cause of FUO was Enteric fever accounting for 6.7% of cases. This is similar to many other studies.[9,18,22,23] The main reason for increased incidence of enteric fever in India is mainly due to inadequate sanitation and poor hygiene. Most cases responded to intravenous Ceftriaxone therapy, which is the first line drug for Enteric fever. In spite of widespread vaccination campaigns against Typhoid, still, there is a rising trend in the incidence of Enteric fever mainly because of poor town planning, population expansion and poor vaccination rates.

In the undiagnosed group (4% of FUO), one child exhibited a clinical course similar to a viral illness and eventually resolved spontaneously. Though two cases had a course similar to enteric fever their diagnosis could not be proven. The fever resolved with an empirical therapy with third generation cephalosporin. Several series have reflected this trend with undiagnosed groups contributing 10-30% of all cases in children.[2,3,9,10,13,16]

A majority of the cases (85%) were diagnosed by serology, blood and urine culture. The tests that have been performed as a routine in all patients had a very poor diagnostic yield in contrast to tests that have been done based on some clinical or laboratory indication. There was a lesser yield for the blood culture noticed in this study. One probable reason for a relatively lesser yield of blood culture may be the prior initiation of antibiotics in the primary care centers before coming to tertiary care centre.

A primary concern of the pediatricians in evaluating a child with FUO should be limited use of investigations that are case-specific especially in developing countries such as India where availability and affordability are the limiting factors. Hence, formulation of regional guidelines for evaluation of children with FUO would be useful in this regard. Data from our study would be useful to formulate such regional guidelines and management strategies for children presenting with fever of >8 days. Our study has some limitations. The study was a hospital based study. The sample may not be representative of the entire community. For children in whom a definitive diagnosis could not be reached, work up for viral etiologies could not be done due to economical constraints (especially EBV).

To conclude, infections have been found to be the most common etiological factor for FUO in children in South India. Scrub (Rickettsial) typhus was the leading cause of the infections diagnosed. Initiation of relevant investigations and targeted antimicrobial treatment in the management of fever and familiarizing primary care physicians about the common causes of FUO are the key elements in the diagnosis and management of FUO in developing countries Further studies done at multiple centers and community level would be necessary to see if the results of the present study are replicable. If similar data is found, regional guidelines can be formulated for workup and management of a child with FUO >8 days.

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