RESEARCH ARTICLE

Profile of Fever of Unknown Origin in Children and the Role of Investigation: An Observational Study

P. Aparna Reddy, M. Shravani Reddy

Rainbow Children's Hospital, Hyderabad, India

ABSTRACT

Objectives: Fever of Unknown Origin (FUO) in children remains difficult to diagnose. This prospective, observational study aimed to determine the clinico-etiological profile and the role of clinical procedures in establishing the diagnosis.

Methods: Children (between 1 month and 16 years) with prolonged fever meeting the criteria of FUO were included. A detailed medical history, physical examination and laboratory tests were conducted according to an algorithm (phase I-III). Clinical procedures that were useful in obtaining final etiology were evaluated.

Results: In total, 69 children were enrolled, categorized into five groups based on etiology of FUO. Infections (31.8%) were the leading cause followed by malignancy (20.2%), connective tissue disorder and miscellaneous conditions (14.5%); undiagnosed patients (18.8%) had either a spontaneous resolution or incomplete workup. Duration of fever was 20-60 days, longer in malignancies, least in infections and mean ± SD duration between admission and a definitive diagnosis was 5.65 ± 1.06 days. Tuberculosis was the most common among the infections, systemic onset juvenile idiopathic arthritis and Common acute lymphoblastic leukemia antigen positive B cell acute lymphoblastic leukemia were common causes of connective tissue disorder and malignancy, respectively.

The diagnosis was established by Phase II (33.3%) and Phase III (34.8%) investigations. Non-invasive and invasive investigations were useful in 56.3%, and 43.7 %, respectively.

Conclusions: Infections are the most common cause of FUO in children followed by malignancy. A stepwise approach is useful in diagnosis. Infections and connective tissue disorders are diagnosed by non-invasive investigations while malignancy and miscellaneous conditions by invasive investigations. Focused clinical and diagnostic approach is mandated. *J Microbiol Infect Dis 2019; 9(3):137-143.*

Keywords: *Acute lymphoblastic leukemia, algorithm, children, fever of unknown origin, children*

INTRODUCTION

Fever of Unknown Origin (FUO) is one of the common clinical situations but the most challenging for the physician and often exhausting due to the requirement of elaborate diagnostic workup involving numerous procedures, which can sometimes fail to reveal the etiology [1,2].

The incidence of FUO ranges from 0.5% to 3% [3,4]. There are well over two-hundred different reported causes of FUO [5]. To date, there are no well-designed published guidelines or evidence based recommendations and no gold standard diagnostic workup of FUO [6]. The general direction of evaluation varies based on patient presentation, geographic location, associated symptoms, environmental exposures, physician experience, and available testing techniques.

Changing clinical scenario in terms of varied clinical presentation and control of common infections and communicable diseases brought some uncommon etiology into focus. Identifying the etiology is not only useful in the management but also in the prevention of disease complications. Our study aimed to develop an insight into the causes of FUO in children and evaluated the clinical procedures useful in establishing the diagnosis.

METHODS

This was a prospective observational study conducted at a tertiary care hospital between

May 2012 and April 2016 after obtaining approval from the Institutional Ethics Committee. This study was approved by the Institutional Ethics Committee, Rainbow Children's Hospital, Hyderabad, India. Children aged 1month-16 years admitted with FUO were included in the study; children with previously known immunosuppressive disease and suspected nosocomial infection were excluded [7].

After obtaining a written informed consent a detailed medical history and physical examination was done. Investigations were conducted according to an algorithm (Figure 1) and need basis. We followed a three stage FUO protocol in the patient assessment [8]. After evaluation, children were categorized according to the etiology of fever into that due to infection, connective tissue disorders, malignancy, miscellaneous conditions and undiagnosed fever.
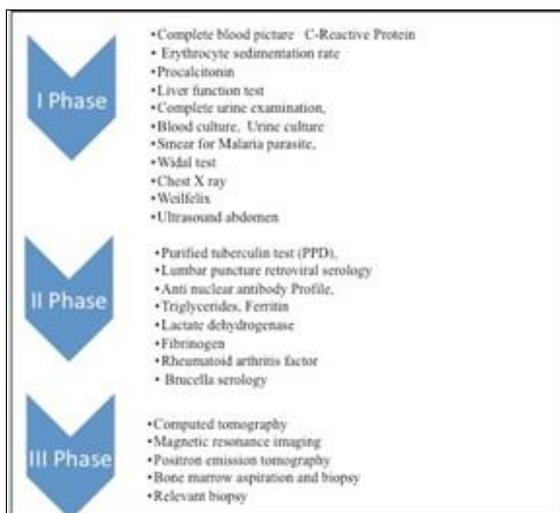

Figure 1. Step-wise investigations.

Statistical Analysis

The descriptive statistics was used; results were expressed as mean, standard deviation for continuous variables, and median, interquartile range (IQR), and percentage (%) distribution for categorical variables. Tables and figures were used as appropriate. Statistical analysis was performed using SPSS, 20th version).

RESULTS

Sixty-nine children meeting the study criteria were included. There were 40 (58%) males and 29 (42%) females. The mean ± SD age of presentation was 82 ± 52.4 months (6.8 years ±

4.4), range of 1-16 years and median of 6.25 years.

Of 69 children, 33 (48%) presented only with fever and 36 (52%) with fever along with symptoms; joint pains (n=10, 27.7%), cough (n=6, 16.6%), maculopapular rash (n=3, 8.3%), weight loss (n=7, 19.4%). Other non-specific symptoms (headache, vomiting, and pain abdomen) were seen in ten (27.7%) children.

The diagnosis of FUO was established in fifty-six (81.2%) children. Infections (n=22, 31.8%) malignancy (14, 20.2%) were the common causes (Figure 2). Bacterial infections were diagnosed in 16 cases (72.7%), viral in 3 (13.6%) and protozoal in 03 (13.6%) as etiological factors. Table 1 shows various causes of FUO among different age groups. Those who remained undiagnosed either had a spontaneous recovery or went against medical advice. All children included in the study received prior antimicrobials and 80% of children referred from other hospitals.

Median duration of fever before admission was 28 days and interquartile range of 20-60 days, highest in malignancies (60 days) and least in infections (26 days). Mean duration between admission and definitive diagnosis was 5.65 days ± 1.06 days. Etiology was established within a week of admission, connective tissue disorders and malignancy was identified faster (5 days) (Figure 2).

Tuberculosis (8/22, 36.4%, pulmonary four 4, extrapulmonary 4), brucellosis (three cases, 13.6%) and rickettsia (3 cases, 13.6%) were the common infections. Mean duration of fever in infections is 25.8 days. Median duration of fever among tuberculous patients was 21 days, with IQR 20-22 days. Common acute lymphoblastic leukemia antigen (CALLA) positive B cell acute lymphoblastic leukemia (ALL) was most common malignancy diagnosed (n=8). Among connective tissue disorders, systemic onset juvenile idiopathic arthritis (8), and systemic lupus erythematosus (2) were common. Mean duration of fever in malignancies was 59.8 days, 36.5 days for connective tissue disorders, 46.5 days for miscellaneous causes, and 39 days among those who remained undiagnosed.

Non-invasive and invasive investigations aided in establishing the diagnosis in 31(56.3%) and 25 (43.7%) children, respectively (Figure 3).

Complete blood picture (CBP) was abnormal in 73.9% with 50.7% children with Hemoglobin< 10gm/dl. High C-reactive protein (CRP)>10 was found in 72.4%, and high erythrocyte sedimentation rate (ESR) more than 10 in 91%. Serum lactate dehydrogenase (LDH) was abnormal in 81.5%.

Table 2 and 3 show the causes of FUO identified at different level of investigation among the study population.

Treatment and follow up

Patients received treatment according to the diagnosis and as per the hospital treatment protocol. Antibiotics for the bacterial infections and anti-tubercular drugs for tuberculosis, chemotherapy for those with malignancy, non-steroidal anti-inflammatory drugs for those with connective tissue disease. Steroids were given as appropriate. None had fever at the time of discharge.

DISCUSSION

Availability of new diagnostic techniques has expanded the horizon of diseases resulting in narrowing/widening of spectrum of etiology of FUO. Infectious diseases still are focus areas in the etiology of fever in developing countries though non-communicable causes such as malignancy, connective tissue disease are also on the rising trend. However, despite the recent advances in diagnostic techniques FUO remains a formidable challenge. Factors such as geography, age of the patients, socioeconomic factors, availability and accessibility to health care facility have a significant role in FUO [6]. Hence, establishing etiology is crucial in the management of the child with FUO.
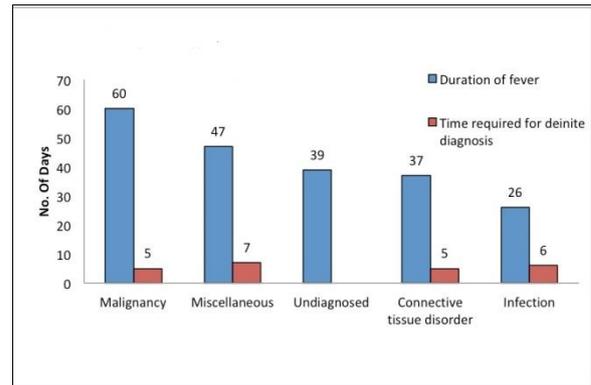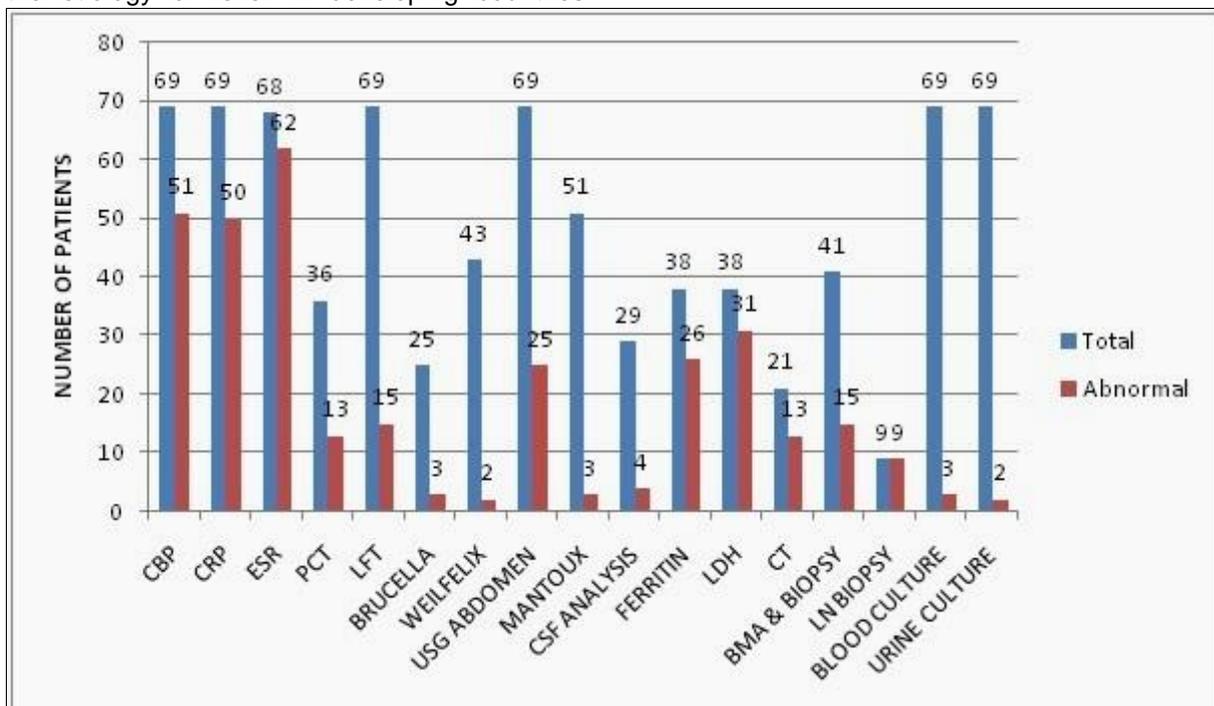

Figure 2. Comparison of duration of fever before hospitalization and time taken for diagnosis after hospitalization.

CBP= Complete Blood Picture; CRP= C-Reactive Protein; ESR= Erythrocyte Sedimentation Rate; PCT= Procalcitonin; LFT= Liver function tests; LDH= Lactate dehydrogenase; CSF analysis= Cerebrospinal fluid analysis; CT= Computed Tomography; LN biopsy = Lymph node biopsy.
Figure 3. .Investigations aided in establishing diagnosis.

Table 1. Etiology of FUO among different age groups

Cause	<1 year	2–5 years	>5-10 years	10-16 years	Total
Infectious disease	1	7	9	5	22
Malignancy	0	3	9	2	14
Collagen vascular disease	0	5	2	3	10
Miscellaneous	0	4	2	4	10
Undiagnosed	1	6	1	5	13
Total	2 (2.9%)	25 (36.2%)	23 (33.3%)	19 (27.5%)	69

Table 2. Etiologies of FUO identified by stepwise investigation process.

Phase	Investigations	Diagnosis	n (%)
I	CBP, CRP, ESR, Blood culture, Urine culture, Widal test, Chest X-ray, Weil Felix	Infections	9 (13.0%)
II	Purified tuberculin test, Retroviral serology, ANA profile, LDH, Ferritin, Brucella antibody	Infections, Connective Tissue Diseases, Miscellaneous conditions	23 (33.3%)
III	Bone-marrow aspiration & biopsy, CT, Lymph node biopsy, Colonoscopy	Infections, Malignancy, Miscellaneous conditions	24 (34.8%)

CBP=Complete blood picture, CRP=C-reactive protein, ESR=Erythrocyte sedimentation rate, ANA =Antinuclear antibody, LDH=lactate dehydrogenase, CT=Computed tomography

Table 3. Aetiology of FUO among study population.

Etiology	n	Phase of Investigation
Infections		
Tuberculosis	8	II, III
Brucella	3	I,II
Rickettsia	3	I
Urinary tract infection	2	I
Dengue fever with secondary HLH	2	I,III
Salmonella infection	1	I
Retroviral infection	1	II
Liver abscess	1	I
Pneumonia with secondary HLH	1	I,III
Connective tissue disorders		
SOJRA	8	II
SLE	2	II
Malignancy		
CALLA positive B cell ALL	8	III
Hodgkins lymphoma	2	III
Non Hodgkins lymphoma	2	III
T cell ALL	1	III
AML	1	III
Miscellaneous		
Inflammatory bowel disease	3	III
Primary immunodeficiency	2	III
Inflammatory myositis	1	II
Auto inflammatory syndrome	1	II
HLH	1	II, III
Kikuchi disease	2	III
Undiagnosed	13 (18.8%)	
Total	69	

HLH= Hemophagocyticlymphohistiocytosis

Our study population had male preponderance (58.0%), a similar observation reported by Chien et al [1]; mean age at presentation was 6.8 years, which is higher compared to the study by Hassan RH et al (5 year 4 months, 5 months-14 years) [9] but lower compared to the study by Chien YL et al [1]. Mean duration of fever before admission was 39 ± 33 days in our study, higher than that reported by Hassan RH et al (32 days, 18-5 years) [9]. Time taken to arrive at a definite diagnosis was <1 week in our study, a longer time for the same was reported by Hassan RH et al [9].

The general pattern of FUO in our study is comparable to previous studies of children in developing countries (2,10-11), diagnosis was established in 56 (81.2%) children. Chien YL et al established the diagnosis in 84.9% of study population [1] in contrast to 63.2% in 1978 [12] Sandoval C et al established diagnosis in 67.9% in 2014 [13].

We report infections (31.8%) and malignancies (20.2%) as the most common followed by connective tissue disorder, miscellaneous and undiagnosed causes. This pattern is similar to the previous reports [1,14,15]. Infections retained their first place in the list as reported by Cruz Guerrero G et al [12] since 1978 (64.5%), though there is a reduction. Sandoval C et al [13] report a similar order of infections (88.4%), malignancy (4.8%), rheumatologic (4.8%) and Kawasaki disease (2.8%). Enteric fever and urinary tract infections were common among infections. In our study, bacterial infections (72.7%) were common compared to viral (13.6%) tuberculosis is the most common cause (36.36%) similar to the previous reports [11,12]. Three patients each had brucellosis and rickettsial disease. Our observations support inclusion of brucellosis in differential diagnosis [16], and ricketsial disease as reported by Chien YL et al [1] Children with infectious diseases received a course of antibiotics prior to hospitalization.

Malignancies were the second most common cause of FUO in our study; CALLA positive B cell ALL (57.14%), Hodgkin's lymphoma (14.23%), Non-Hodgkin's lymphoma (14.2%) were frequent. Previous reports placed malignancies in the 3rd place as a cause of FUO, of late has jumped to 2nd place replacing collagen vascular disorders [1]. ALL was the most common among malignancies in children presenting as FUO [1] and our study is in support of this.

Undiagnosed causes are the most challenging cases worldwide. Kim et al [17] faced this challenge in 43% of their patients and accounted for 18.84% in our study. A recent study from our country reported that only 12.0% cases remained undiagnosed. This could be due to smaller number of patients with shorter duration of fever [18]. Chien YL et al [1] report 15.05% patients remained undiagnosed. Pediatricians have to focus on this area for betterment. Clinical judgment and optimal use of available modern diagnostic facilities is highly recommended. It is necessary that the pediatrician should be adequately trained to identify the cause of the fever.

Crump JA et al [19] reported bacterial and fungal blood borne infections (3.4%) and bacterial zoonosis (20.2%). *Salmonella typhi* (25.9%) and *Streptococcus pneumoniae* (22.2%) were bacterial blood borne infections; brucellosis (2.0%), leptospirosis (7.7%), spotted fever group rickettsioses (7.4%) and Q fever (2.6%) were reported bacterial zoonotic infections. Malaria was clinically diagnosed in 60.4% but was established only in 1.3%.

Physical examination is an essential tool in the diagnosis and is mandated. Skin rashes, visible nodules in the neck, mass in the abdomen often lead to the diagnosis. Diagnosis is based on 3 stage protocol as universally practiced. We established diagnosis in <7 days in 100% patients; infectious diseases were diagnosed by stage I & II, malignancies at stage III and miscellaneous by stage II & III investigations. Non-invasive investigations proved valid in 56.3% while non-invasive in 43.7% children. Tuberculosis and malignancy required a battery of investigations to confirm the diagnosis, while the miscellaneous causes required exhaustive laboratory investigations.

All our patients had complete resolution except for those who were discharged against medical advice and lost to follow up (n=4.5. 7%).

Sandoval C report complete resolution in 98% [13]. There was no mortality in our study.

Utility of investigations in diagnostic process

Inspite of high range of abnormality in CRP, ESR, LDH, serum ferritin none of these directly led to a diagnosis but together aided in diagnosis of infections and connective tissue diseases supporting the observation of Xie T et al. [20]. Apart from the standard investigations for tuberculosis, Brucella serology, blood culture, urine culture found to be effective in infectious diseases. Our study indicated the diagnostic role of Bone marrow aspiration and biopsy (n=41) that led to final diagnosis in all; it was useful in diagnosing malignancies, hemophagocytic lymphohistiocytosis (HLH), infections, supporting the views of Labrador J et al. [21]. We found Lymph node biopsy as another useful diagnostic tool. Of the imaging techniques CT (chest/abdomen) was the most useful investigation. Chest X ray and USG abdomen were inconclusive and did not contribute to a final diagnosis, similar to the report by Steele RW et al. [22].

First line of investigations were useful in only in infections, but gave a clue for further workup in other etiologies of FUO. Malignancies and miscellaneous conditions required third line of investigations.

Conclusion

FUO remains one of the challenging clinical entities among pediatric patients despite the availability of advanced investigational tools. Establishing etiology in these cases still poses a challenge. Infections with tuberculosis the most common are still in the top of the list of etiologies of FUO. Non-invasive investigations are helpful for the diagnosis of Infections and connective tissue disorders while Invasive investigations are required to establish the diagnosis of malignancy and miscellaneous conditions. Clinical judgment supported by step up investigations is essential in establishing the diagnosis. Undiagnosed cases ended up in spontaneous resolution or incomplete workup as they went against medical advice.

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